A.M.A. Archives OF
INTERNAL MEDICINE

HEADACHE AND HYDRATION
ADRIAN M. OSTFELD, M.D., ET AL.

THE EFFECT OF INTRAVENOUS DEMECOLCINE (COLCEMID) ON ACUTE GOUT
WILLIAM C. KUZELL, M.D., ET AL.

THE DIAGNOSIS OF BRONCHOGENIC CARCINOMA IN PATIENTS WITH PULMONARY TUBERCULOSIS
MORTON E. SHAFRAN, M.D., ET AL.

THE USE OF CHLORPROMAZINE IN THE MANAGEMENT OF PATIENTS WITH HEAD INJURY
JAMES G. SHEA, M.D., ET AL.

MARKED HYPERNATREMIA AND HYPERCHLOREMIA WITH DAMAGE TO THE CENTRAL NERVOUS SYSTEM
SAMUEL NATELSON, Ph.D., ET AL.

THE HAZARD OF UNRECOGNIZED CATHETERIZATION OF THE CORONARY SINUS
JOHN L. READ, M.D., ET AL.

LOCULATED INTERLOBAR PLEURAL EFFUSION DUE TO CONGESTIVE HEART FAILURE
JOHN A. HIGGINS, M.D., ET AL.

STUDIES ON URINARY LIPASE
MARTIN M. NOTHMAN, M.D., ET AL.

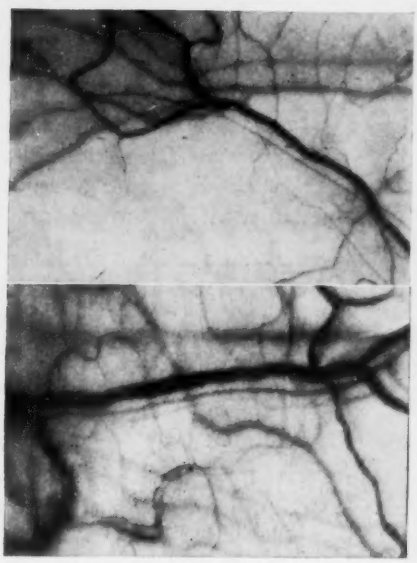
TUBERCULOUS PLEURISY WITH EFFUSION
J. ARTHUR MYERS, M.D.

SENILE OSTEOPOROSIS
MARC MOLDAWER, M.D.

COMPLETE CONTENTS ON FIRST PAGE

AUGUST 1955
VOLUME 96 NUMBER 2

From Ostfeld et al., p. 142



AMERICAN MEDICAL ASSOCIATION Publication

you can prevent attacks of angina pectoris

Peritrate, a long-acting coronary vasodilator, has repeatedly demonstrated its effectiveness in preventing attacks of angina pectoris in 4 out of 5 cases.[1,2,3]

Prophylaxis with Peritrate results in fewer, less severe attacks, reduced nitroglycerin dependence, improved EKG's where abnormal patterns exist and increased exercise tolerance.

Peritrate's action is similar to that of nitroglycerin but considerably more prolonged... "favorable action [can] be elicited for 5 hours or more after its administration."[4]

Usual dosage is 10 to 20 mg. *before meals* and at bedtime.

The specific needs of most patients and regimens are met with Peritrate's various dosage forms. Peritrate is available in both 10 and 20 mg. tablets; Peritrate Delayed Action (10 mg.) allows uninterrupted continuation of protection through the night.

References:
1. Winsor, T., Humphreys, P.: Angiology *3*:1 (Feb.) 1952.
2. Plotz, M.: N. Y. State J. Med. *52*:2012 (Aug. 15) 1952.
3. Dailheu-Geoffroy, P.: L'Ouest-Médical, vol. 3 (July) 1950.
4. Russek, H. I., *et al.*: Am. J. M. Sc. *229*:46 (Jan.) 1955.

Peritrate®

tetranitrate

(brand of pentaerythritol tetranitrate)

WARNER-CHILCOTT

TABLE OF CONTENTS

VOLUME 96 AUGUST 1955 NUMBER 2

EDITORIALS

PAGE

Vitamania, Polypharmacy, and Witchcraft 137

ORIGINAL ARTICLES

Headache and Hydration

Adrian M. Ostfeld, M.D.; Donald J. Reis, B.S.; Helen Goodell, B.S., and Harold G. Wolff, M.D., New York 142

The Effect of Intravenous Demecolcine (Colcemid) on Acute Gout

William C. Kuzell, M.D.; Ralph W. Schaffarzick, M.D., and W. Edward Naugler, M.D., San Francisco 153

The Diagnosis of Bronchogenic Carcinoma in Patients with Pulmonary Tuberculosis

Morton E. Shafran, M.D., Chincoteague, Va., and Julius Kavee, M.D., New York 157

The Use of Chlorpromazine in the Management of Patients with Head Injury

James G. Shea, M.D.; Ralph W. Alman, M.D., and Joseph F. Fazekas, M.D., Washington, D. C 168

Marked Hypernatremia and Hyperchloremia with Damage to the Central Nervous System

Samuel Natelson, Ph.D., and M. O. Alexander, M.D., Rockford, Ill 172

The Hazard of Unrecognized Catheterization of the Coronary Sinus

John L. Read, M.D.; Edward G. Bond, M.D., and Reno R. Porter, M.D., F.A.C.P., Richmond, Va 176

Loculated Interlobar Pleural Effusion Due to Congestive Heart Failure

John A. Higgins, M.D.; John L. Juergens, M.D.; André J. Bruwer, M.D., and Thomas W. Parkin, M.D., Rochester, Minn 180

Studies on Urinary Lipase

Martin M. Nothman, M.D.; Joseph H. Pratt, M.D., and Allan D. Callow, M.D., Boston 188

Tuberculous Pleurisy with Effusion

J. Arthur Myers, M.D., Minneapolis 191

TREATMENT IN INTERNAL MEDICINE

Senile Osteoporosis

Marc Moldawer, M.D., Boston 202

PROGRESS IN INTERNAL MEDICINE

Diabetes Insipidus

J. Floyd Cannon, M.D., Salt Lake City 215

CASE REPORTS

Refractory Hypotension Following Removal of Pheochromocytoma

Earl F. Beard, M.D.; Donald B. Butler, M.D., and Harvey S. Rosenberg, M.D., Houston, Texas 273

Toxic Nephrosis and Massive Hepatic Necrosis Produced by Urethan

John F. Flanagan, M.D., Emory University, Ga 277

REGULAR DEPARTMENTS

News and Comment 281

Books 283

A. M. A.
ARCHIVES OF INTERNAL MEDICINE

VOLUME 96 AUGUST 1955 NUMBER 2

COPYRIGHT, 1955, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

PAUL S. RHOADS, Chief Editor, Chicago

WILLIAM B. BEAN, Iowa City
ARTHUR BLOOMFIELD, San Francisco
GEORGE E. BURCH, New Orleans
HUGH R. BUTT, Rochester, Minn.
CHARLES S. DAVIDSON, Boston
LOUIS LEITER, New York
BRUCE K. WISEMAN, Columbus, Ohio

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

AMERICAN MEDICAL ASSOCIATION
Scientific Publications

The Journal of the American Medical Association. Weekly. Annual Subscription Price, $15.00.

Quarterly Cumulative Index Medicus. Issued Twice a Year. Subscription Price, Calendar year, $20.00.

A. M. A. Specialty Journals
Monthly

A. M. A. Archives of Internal Medicine. Paul S. Rhoads, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $10.00; Canada, $10.50; Foreign, $11.50; individual copy, $1.00.

A. M. A. Archives of Dermatology. Paul A. O'Leary, M.D., Chief Editor, 200 First St. S.W., Rochester, Minn. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Ophthalmology. Francis Heed Adler, M.D., Chief Editor, 313 S. 17th St., Philadelphia 5. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Surgery. Waltman Walters, M.D., Chief Editor, American Medical Association, 535 N. Dearborn St., Chicago 10. Price, $14.00; Canada, $14.50; Foreign, $15.50; individual copy, $1.25.

A. M. A. American Journal of Diseases of Children. Robert Barrett Lawson, M.D., Chief Editor, 1000 N.W. 17th St., Miami 36, Fla. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Pathology. Paul R. Cannon, M.D., Chief Editor, Department of Pathology, University of Chicago, The School of Medicine, 950 E. 59th St., Chicago 37. Price, $8.00; Canada, $8.50; Foreign, $9.25; individual copy, $1.00.

A. M. A. Archives of Neurology and Psychiatry. Tracy J. Putnam, M.D., Chief Editor, 450 N. Bedford Drive, Beverly Hills, Calif. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Otolaryngology. George M. Coates, M.D., Chief Editor, 1721 Pine St., Philadelphia 3. Price, $12.00; Canada, $12.50; Foreign, $13.50; individual copy, $1.25.

A. M. A. Archives of Industrial Health. Prof. Philip Drinker, Chief Editor, Dept. of Industrial Hygiene, Harvard University School of Public Health, 55 Shattuck St., Boston 15. Price, $8.00; Canada, $8.50; Foreign, $9.00; individual copy, $1.00.

Check, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

Published Monthly by

AMERICAN MEDICAL ASSOCIATION

535 NORTH DEARBORN STREET • CHICAGO 10, ILLINOIS

Entered as Second Class Matter Jan. 23, 1909, at the Postoffice at Chicago, Under the Act of March 3, 1879. Annual Subscription, $10.00

All of the following articles have appeared in TODAY'S HEALTH and are now available in pamphlet form.

ALCOHOLISM

an

important

problem

in today's living

ALCOHOLICS ANONYMOUS

Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.
4 pages, 10 cents

ALCOHOL AND CIRRHOSIS OF THE LIVER

Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences.
by Russell S. Boles
4 pages, 10 cents

HOW TO HELP A PROBLEM DRINKER

Understanding the alcoholic's capabilities, the necessity of help, causes of his condition.
by Edward A. Strecker and Francis T. Chambers, Jr.
4 pages, 10 cents

THE TREATMENT OF ALCOHOLISM

Tracing the steps from convincing the alcoholic that he is sick through treatment and cure.
by Lewis Inman Sharp
4 pages, 10 cents

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM

Its place among methods of treatment today, its development and correlation with personality factors.
by Walter L. Voegtlin
4 pages, 10 cents

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM

Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel.
by E. H. L. Corwin
4 pages, 10 cents

THE ABOVE SIX PAMPHLETS ARE ALSO AVAILABLE IN BOOKLET FORM FOR ONLY 50 CENTS

HOW TO MEASURE DRUNKENNESS

A partial transcript of an actual courtroom case.
H. A. Heise
8 pages, 10 cents

ADDRESS REQUESTS TO:

BUREAU OF HEALTH EDUCATION
AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

Instructions to Contributors

Communications regarding editorial management, subscriptions, reprints, etc., should be addressed to Specialty Journals, American Medical Association, 535 North Dearborn Street, Chicago 10.

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor of the Specialty Journal concerned. Articles are accepted for publication on condition that they are contributed solely to that journal.

An original typescript and the first carbon of an article should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. An article in English by a foreign author should be accompanied by a draft in the author's mother tongue. Improvised abbreviations should be avoided.

The main title of an article may not contain more than seventy characters and spaces; a subtitle may be of any length. The subtitle should be sufficiently detached from the main title that a punctuation mark as strong as a colon can be used in the Table of Contents to separate it from the main title; it must not begin with "with."

The author's name should be accompanied by the highest academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

Typographic considerations necessitate that the first paragraph of an article contain not fewer than thirty words. A Case Report must be preceded by an introductory paragraph containing at least thirty words before the details of the case are given.

Material quoted from another publication must be quoted exactly if the original is in English—spelling, capitalization, punctuation, etc., unchanged. Material taken largely from another publication must be credited to the original author, whether quoted exactly or merely abstracted. If such material is quoted indirectly, the author must be careful to leave no complete sentence of the original unaltered. Use of uncredited quotations will be sufficient cause for rejection of an article.

Each article should be accompanied by a summary in the present tense, presenting the main points of the article, but in somewhat more generalized terms than in the article itself.

If it is necessary to publish a recognizable photograph of a person, the photograph must be accompanied by written permission of the subject himself if an adult, or of the parents or guardian if a child, to publish his photograph. An illustration which has been published in another publication must be accompanied by written permission from the author and the original publisher to reproduce it in an A. M. A. Specialty Journal.

The maximum illustration allowance is ten illustrations within a total of 100 sq. inches or $100, whichever is of greater advantage to the author. When no restrictions are placed by the author upon cropping, reducing, and grouping, the publisher is often able to use twenty or more illustrations in one article with the $100 allowance. Submit sharp prints of the following sizes, 2½″ wide × 2½″ or 3½″ high, 3½″ wide × 2½″ high, and 5½″ or 7″ wide × 3½″ high, to minimize reduction and/or cropping. Oversized originals should be photographed and a print submitted. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author.

Any cut-off marks should be made on the margins or mountings rather than on the illustration itself. Charts and drawings should be in black ink on hard, white paper. Lettering must be large enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, an abbreviated title of the article, and top plainly indicated. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. IT IS PREFERRED THAT ILLUSTRATIONS BE UNMOUNTED.

References to the literature should be numbered in the order in which they are referred to in the text or listed in alphabetical order without numbers. A chronological arrangement, with all entries for a given year alphabetized according to the surname of the first author, may be used if preferred. References should be typed on a special page at end of manuscript. They should conform to the style of the Quarterly Cumulative Index Medicus, and must include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. Names of periodicals should be given in full or abbreviated exactly as in the Quarterly Cumulative Index Medicus. Reference to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication. Titles of foreign articles, if originally in a generally known Romance or Germanic tongue, must either all be in English translation or all be in the original language. Titles in other languages must be translated. The author must assume responsibility for the accuracy of foreign titles.

Matter appearing in the A. M. A. Specialty Journals is covered by copyright, but as a rule no objection will be made to its reproduction in a reputable medical journal if proper credit is given. However, the reproduction for commercial purposes of articles appearing in the A. M. A. Specialty Journals, or in any other publications issued by the Association, will not be permitted.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

Enriched Bread...

Low Cost Insurance Against Nutritional Ills

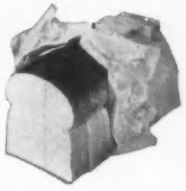
In recent years the improved pattern of foods consumed in the United States has largely eliminated frank forms of nutritional deficiency diseases. This great gain in public health is attributable in large measure to the nationwide distribution of nutritionally improved staple foods, well exemplified by enriched bread.[1] "Such improvement of foods in the United States has been described as low-cost insurance against nutritional ills."[2,3]

Present-day enriched white bread, enhanced in B vitamins, minerals, and milk protein content, serves as an important nutritional protection to consumers. In particular, low-income groups, who eat large amounts of enriched bread because of its low cost, benefit by its high nutritional values.[3]

Wherever sold, enriched bread complies with the federal definition and standard for the product. Per pound, enriched bread provides at least 1.1 mg. of thiamine, 0.7 mg. of riboflavin, 10 mg. of niacin, and 8 mg. of iron. By and large, it also supplies about 400 mg. of calcium and 39 grams of protein. Since the protein consists of flour and milk proteins, it is biologically effective for growth as well as tissue maintenance. Enriched bread is one of the reasons why "We are a nation . . . fed on a plane of nutrition unequalled anywhere in the world."[4]

1. King, C. G.: Newer Concepts of Optimum Nutrition, Food Technol. *8*:486 (Nov.) 1954.
2. U.S. National Office of Vital Statistics: Vital Statistics of the United States, 1948. Part I. Washington, D.C., U.S. Government Printing Office, 1950.
3. Sebrell, W. H.: Developing Modern Nutrition Programs, Public Health Reports, United States Department of Health, Education, and Welfare *69*:277 (Mar.) 1954.
4. Josephson, D. V.: Review of Chemical Mechanisms Affecting Flavor Acceptability of Dairy Products, J. Agr. & Food Chem. *2*:1182 (Nov.) 1954.

The nutritional statements made in this advertisement have been reviewed and found consistent with current medical opinion by the Council on Foods and Nutrition of the American Medical Association.



AMERICAN BAKERS ASSOCIATION

20 NORTH WACKER DRIVE • CHICAGO 6, ILLINOIS

now available
for clinical use...

METICORT

"possesses an augmented therapeutic ratio"[1]
in cortical hormone therapy

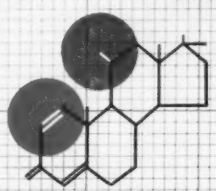
Schering

METICORTELONE possesses antirheumatic and anti-inflammatory effectiveness and hormonal properties similar to those of METICORTEN,[1-5] the first of the new Schering corticosteroids. Both are three to five times as potent, milligram for milligram, as oral cortisone or hydrocortisone. METICORTELONE and METICORTEN therapy is seldom associated with significant water or electrolyte disturbances.

METICORTELONE is an analogue of hydrocortisone, as METICORTEN is of cortisone. The availability of these new steroids, both discovered and introduced by Schering, provides the physician with two therapeutic agents of approximately equal effectiveness.

METICORTELONE is now available as 5 mg. buff-colored tablets, scored, bottles of 30 and 100. In the treatment of rheumatoid arthritis, dosage begins with an average of 20 to 30 mg. (4 to 6 tablets) a day. This is gradually reduced by 2.5 to 5 mg. until daily maintenance dosage, which may be between 5 to 20 mg., is reached. The total 24-hour dose should be divided into four parts and administered *after meals and at bedtime.* Patients may be transferred directly from hydrocortisone or cortisone to METICORTELONE without difficulty.

elone



PREDNISOLONE, SCHERING (metacortandralone)

Bibliography: (1) Bunim, J. J.; Pechet, M. M., and Bollet, A. J.: J.A.M.A. *157*:311, 1955. (2) Waine, H.: Bull. Rheumat. Dis. *5*:81, 1955. (3) Tolksdorf, S., and Perlman, P.: Fed. Proc. *14*:377, 1955. (4) Herzog, H. L., and others: Science *121*:176, 1955. (5) King, J. H., and Weimer, J. R.: Experimental and clinical studies on METICORTEN (prednisone) and METICORTELONE (prednisolone) in ophthalmology, A.M.A. Arch. Ophth., to be published. (6) Boland, E. W.: California Med. *82*:65, 1955; abs. Curr. M. Digest *22*:53, 1955. (7) Dordick, J. R., and Gluck, E. J.: J.A.M.A. *158*:166, 1955. (8) Margolis, H. M., and others: J.A.M.A. *158*:454, 1955. (9) Barach, A. L.; Bickerman, H. A., and Beck, G. J.: Dis. Chest *27*:515, 1955. (10) Arbesman, C. E., and Ehrenreich, R. J.: J. Allergy *26*:189, 1955. (11) Skaggs, J. T.; Bernstein, J., and Cooke, R. A.: J. Allergy *26*:201, 1955. (12) Schwartz, E.: J. Allergy, *26*:206, 1955. (13) Robinson, H. M., Jr.: J.A.M.A. *158*:473, 1955. (14) Dordick, J. R., and Gluck, E.: Preliminary Clinical trials with prednisone (METICORTEN) in systemic lupus erythematosus, A.M.A. Arch. Dermat. & Syph., in press. (15) Nelson, C. T.: J. Invest. Dermat. *24*:377, 1955.

first of the new Schering corticosteroids.

METICORTEN

PREDNISONE, SCHERING (metacortandracin)

- replacing the older corticosteroids in rheumatoid arthritis[1,2,6-8] intractable asthma[9-12] eye disorders[5] certain skin disorders such as disseminated lupus erythematosus,[13,14] acute pemphigus,[13,15] atopic dermatitis[15] and other allergic dermatoses
- more active than hydrocortisone or cortisone, milligram for milligram
- relatively free of significant water or electrolyte disturbances [5]

METICORTEN is available as 5 mg. scored, white tablets in bottles of 30 and 100.
METICORTELONE,* brand of prednisolone (metacortandralone).
METICORTEN,* brand of prednisone (metacortandracin). ML-J-55 *T.M.

THERAPEUTIC BILE

for patients with liver and gallbladder disorders

confirmed in the laboratory

In the isolated perfused liver (rat), *hydrocholeresis* with *Decholin Sodium* increases bile flow 200 to 300 per cent—*with no increase in total solids.*[2]

(A) *Hydrocholeresis*: Bile capillaries (rabbit liver) are filled with dilute bile 15 minutes after i.v. injection of sodium dehydrocholate.

(B) Untreated control.

Photomicrographs Demonstrate *Hydrocholeresis*: Increased Secretion of Highly Dilute Bile[1]

confirmed in practice

"true hydrocholeresis —a marked increase both in volume and fluidity of the bile"[3]

"Since bile of this nature and in this large output can flush out even the smaller and more tortuous biliary radicles, hydrocholeresis [with *Decholin* and *Decholin Sodium*] aids in removal of inspissated material and combats infection."[3]

Decholin® – Decholin Sodium®

Decholin Tablets (dehydrocholic acid, *Ames*) 3¾ gr. (0.25 Gm.). *Decholin Sodium* (sodium dehydrocholate, *Ames*) 20% aqueous solution; ampuls of 3 cc., 5 cc. and 10 cc.

(1) Clara, M.: Med. Monatsschr. 7:356, 1953. (2) Brauer, R. W., and Pessotti, R. L.: Science *115*:142, 1952. (3) Schwimmer, D.; Boyd, L. J., and Rubin, S. H.: Bull. New York M. Coll. *16*:102, 1953.

63255

AMES COMPANY, INC • ELKHART, INDIANA Ames Company of Canada, Ltd., Toronto

A.M.A. Archives OF
INTERNAL MEDICINE

Editorials

VITAMANIA, POLYPHARMACY, AND WITCHCRAFT

OSCILLATIONS and sudden shifts in the center of gravity of therapeutics have been occurring with increasing frequency during recent years. It is imperative that those responsible for setting standards in medical practice look squarely at the changes. A most impressive advance has been the discovery of many specifics. We have now a number of drugs with great therapeutic power. They may be used for good or ill. A generation of physicians whose orientation fell between therapeutic nihilism and the uncritical employment of ever-changing placebos was ill prepared to handle a baffling array of really powerful compounds. The advent of sulfa drugs; the emergence of effective antibiotics; the transformation of endocrine therapy from a stage only a step in advance of mysticism to one with many hormones available for a great variety of therapeutic manipulations; the isolation of vitamins in bewildering abundance which soon outran the known vitamin-deficiency disorders; the development of drugs with potent but still not completely mapped effects on emotions—all these have made it difficult if not impossible for the most conscientious and critical physician to "keep up" with the torrent which has now become a flood.

To a conspicuous degree this development has been made possible by the applied research which the pharmaceutical industry itself has supported in research institutes connected with individual corporations or in universities and medical schools. The transformations from small laboratory manufacture, through pilot plant, to fabrication of complex chemicals by mass production are costly. The industrial risks are great. In the highly competitive pharmaceutical industry it is natural that each company is anxious to discover new and effective therapeutic agents which can be marketed before others can produce competing items. The managers and directors of such companies have been trained in business, not in the practice of medicine. Even with a scrupulously correct standard of morals and ethics such concerns are in business to make profits. Any humanitarian endeavor to provide salvation for suffering mankind is a secondary aim. The promotion of new drugs is achieved by various kinds of advertising. Let us look at the methods and some implications and possible hazards of present-day practices.

Advertising accepted as legitimate or "ethical" is directed to the physician rather than the layman, pharmacist, or drug store. Neither radio, television, nor newspaper is important. Advertising in journals has been in two classes: (1) that of products approved by the American Medical Association and (2) the others. The stamp of approval was important in giving prestige to the item and manufacturer

and in obtaining revenue for many medical journals by "block booking" of advertising. This seal of approval has been abandoned.

A remarkable feature of drug advertising is seen in the flourishing "throw away" journals. They have achieved great success. Obviously they serve some useful purpose. But useful for whom? Of the major varieties, those which are put out by independent companies not directly promoting the sale of an individual firm's products are open to least objection. There are two kinds of these independent journals. One provides an illustrated synoptical review of a mass of medical literature. It serves as a combination of Reader's Digest and Gallup Poll. The other form, dealing more extensively with practical aspects of the physician's daily life, his business, his office, his laboratory, his taxes, his assistants, ranges between the statistical approach of the Census Bureau and a time-motion study of the doctor's daily life. It includes aspects of medical politics and even medical statesmanship. The journals are profit-making ventures for their owners. They reflect rather than lead medical opinion. Since their support comes from the drug trade, they take a relaxed rather than a conservative view of advertising methods, copy, and taste.

The other major form of journal is that which is published, usually as a monthly, by the larger drug firms. In recent years these have come to combine magnificent medical illustrations, largely in color, with a potpourri of "art" having no necessary relation with medicine or products of the particular pharmaceutical house. Very commonly the articles with illustrations review experiments and experience, particularly that which reports favorably on products of the particular pharmaceutical concern. These lavish and sometimes garish pamphlets pour unsolicited in increasing volume and frequency into the mailbox and across the desk of physicians in this country. And this method of advertising has obviously proved effective. In addition, it gives the less critical and the more time-harried a review of current therapy, warped according to the natural enthusiasms of a manufacturer for his own products. To an alarming degree, this has become the most effective though least desirable form of postgraduate medical education for the general physician in this country today. Less objectionable "house organ" advertising is that from medical book publishers, although they are not likely to use quotations from hostile or critical reviews in their advertising copy.

A natural brother of this form of advertising is the widespread distribution through the mail of an infinite variety of samples. The logistics of distributing this advertising spoor is the despair of the postoffice department. Samples clog the mail room of hospitals and medical schools, cause anguish to the already heavy-laden postman, and are of perennial annoyance to hard-worked secretaries and office assistants. Finally, samples are of such annoyance to many physicians that they resolutely follow the policy of never employing in their practice drugs which reach them in this fashion. These troubles are of a different order from the illness or poisoning which occurs when children, whose exploration and curiosity have not yet been inhibited by caution, take pleasure in satisfying their appetite for medicine by fetching from the mail box or waste basket and eating varying amounts of powerful drugs, some of which are meant for external use only. No one has any clear measure of the extent of damage done along these lines. It is a real problem.

In many respects the mission of the detail man combines the less happy aspect of the evils already outlined. This yeoman, with little professional training, sometimes

a frustrated would-be physician, interested more in sales than in salvation, repeats his patter in an effort to instruct the physician who has not taken the trouble to study medical journals and texts. Such a physician is likely to be beguiled by the lavish contribution of samples for him and his family. The detail man makes no effort to minimize the vast confusion which exists when the same chemical compound is sold under a variety of imaginative, tongue-twisting names dreamed up by someone obsessed with the notion that Latin and Greek stems and roots are very valuable but without the vaguest idea of their actual meaning.

With the coming of specifics therapy has become simplified. The tendency has been for prescriptions to be for single remedies rather than complex mixtures. Writing prescriptions is much less important in the practice of medicine than it was formerly. The ability to get together an unlikely combination of medicaments with no physical incompatibility and probably no therapeutic one either, since they had little specific pharmacologic effect, has been superseded by the use of the single remedy. The problem of the physician, once he has decided which drug to employ, has been to find a sensible time-dose relationship and to determine the method of adminstration. Thus, with the advent of specifics which really could do remarkable things therapeutically, it became easier to direct therapy along sensible lines. The polypharmacy of our medical forebears, outmoded as it had been in fact for a long time, was superseded in practice.

The administration of vitamins has been much abused. It is very confusing to the honest physician. Discovery of many more compounds than the clinicians were able to recognize by specific manifestations of deficiency led to their incorporation in the ubiquitous vitamin tablet. The next step was easy. If some was valuable, more would be still more valuable. So we have witnessed the deplorable state of therapeutic chaos and the seduction of the public into the belief that many of its ills and ails will be improved, its troubles abated if not eliminated, health supercharged to a prodigy of vigor, and other miraculous things happen if only the person eats extra vitamins. And when vitamins really are needed they are apt to be forgotten.

The discoveries in nutrition represent one of the remarkable features of contemporary medicine. To this vast body of knowledge workers in diverse fields and various parts of the world have made contributions. They have helped in the understanding of nutrition and malnutrition. Many of the clinical problems still remain to be investigated. Some of the important ones have scarcely been approached. It seems too hard to pose the proper question in the right context with any likelihood of doing the time-consuming and fearfully expensive studies needed to solve it. Since the mammalian organism generally excretes water-soluble vitamins which are not required, it has been assumed that one could not be harmed by ingesting an overdose of B-complex vitamins. This point has never been established by clinical experiment.

The recent combination of antibiotics with vitamins is a striking example of the returning dangers of polypharmacy and the lapse into the medieval approach towards therapy. While malnutrition may occur under circumstances where antibiotics are appropriately given as remedies, no experimental evidence has been produced to show that fixing the dose of vitamin to the dose of antibiotics by the ligature of questionable advertising is therapeutically sound or theoretically de-

sirable. When any combination of materials is assembled with fixed proportions it is impossible to use the ingredients of the mass-produced product in any other than the fixed ratio. In the second place, the combination of antibiotics and vitamins will inevitably mean that the expense goes up. Many people who require one or the other will not need both. Use of drugs where they are not needed is another factor which adds to the increasing expense of illness without producing commensurate benefit. A clinician who is beguiled by tenuous and theoretical formulations and believes that a single state called malnutrition widely prevails or that a single state of stress exists is succumbing to the widespread and increasing failure to distinguish between the facts, words, and ideas. He is not so much antiintellectual as he is nonintellectual. He reverts to rule of thumb, nickel-in-the-slot therapeutics rather than the thoughtful but difficult employment of individual remedies for individualized problems in individual patients.

Another example of this problem is the combination of two or more antihypertensive drugs. With such products it is impossible to alter the dose of one without altering the dose of the other. Final assignment of the exact role in each powerful antihypertensive drug will not occur for some time. Experienced physicians all agree that it is imperative to be able to vary individual compounds individually. There is no constant ratio which should at all times and for all cases prevail in the combination of two or more antihypertensive drugs. Such a rigid formula will increase the difficulty of handling an already very difficult clinical problem. It will needlessly increase the cost of expensive therapy. It is another example of the manufacturer of drugs trying to do the physician's thinking for him.

Those concerned with expensive placebos have always been distressed that in contemporary American medicine potent, specific therapeutic agents are used much more widely than the known incidence of the appropriate clinical disorder would require. It is common knowledge that when liver extract was the best available therapy for pernicious anemia physicians used many times the amount which would have been adequate to keep all patients with pernicious anemia in the country under good control. Obviously the remedy was used widely for other kinds of anemia and for other disturbances. Sometimes it was a tonic; sometimes, an excuse for "shot therapy." Such practices are bad for several reasons. The misdirection of therapy is wasteful. It may be dangerous. With many very potent compounds the cumulative effects on the human organism from delayed effects which may occur years later cannot be known until sufficient time has elapsed for the problem to be studied. There is no indication that such studies are being done. There is a suggestive evidence that the increased frequency of many so-called collagen diseases may be attributed to a bizarre form of sensitivity reactions to some of the powerful therapeutic agents which are now used so lavishly. The evidence for this is indirect, and there is no proof yet.

The burden of responsibility of leaders in American medicine today goes far beyond that of a previous day when so little specific therapy was available. Medical education should be thorough enough that a well-trained graduate will be able to continue to make his way through the increasing wilderness of new therapeutic agents with some hope of using rational judgment. There is every indication that at the moment beguiling advertising of pharmaceutical houses has to a substantial degree replaced formal graduate medical education concerning therapy. Much of this advertising is perfectly legitimate. There is inevitably a tendency for some to

be bad and for much to err in the direction of promoting the products of doubtful efficacy and of unknown but potential danger. It is necessary for leaders of American medicine and leaders of American drug manufacture to join forces in an effort to see that a tendency to relapse into the mystique of polypharmacy be brought to a quick and complete halt. The time may come when a patient can go through a diagnostic factory where the quantity of various difficulties is titrated mechanically. An answer comes out on ticker tape. This is then run through a vast therapeutical machine which throws just the proper proportion of every needed ingredient into the Mixmaster. This turns out pellets in a neat packet to be grasped by the hopeful but anonymous patient. He then will follow the printed guide, read eagerly like the fortune which emerges from the drugstore scales. Till this millennium comes we must keep up standards. The omens which indicate the direction of therapy today, a reversion to a quasitherapeutical horoscopy, point to a reversion to the polypharmacy which condoned combinations of puppy dog fat, powdered unicorn's horns, dried mosquito wings, and spider webs, obtained from a graveyard in the dark of the moon, and brewed by witches as panacea for real and imagined ills of every kind.

WILLIAM B. BEAN, M.D.

Headache and Hydration

The Significance of Two Varieties of Fluid Accumulation in Patients with Vascular Headache of the Migraine Type

ADRIAN M. OSTFELD, M.D.
DONALD J. REIS, B.S.
HELEN GOODELL, B.S.
and
HAROLD G. WOLFF, M.D., New York

Two kinds of edema have been observed in patients subject to vascular headache of the migraine type. One was a localized fluid accumulation that developed during the headache and occurred primarily in those scalp areas in which headache was experienced. This was featured by tenderness and slight to moderate pitting.

The second was a more generalized fluid accumulation that commonly developed before the headache, involved many parts of the body, and was demonstrable by weight gain and pitting of dependent body areas.

Data about the latter type were recently analysed by Schottstaedt and Wolff,[1] who indicated that headache and widespread fluid retention were often concomitant but not causally related phenomena. Their data showed that there was frequently a retention of sodium, potassium, and water before the headache and a diuresis during the phase of dwindling intensity of the headache.

The present studies were undertaken to determine the frequency, magnitude, and natural history of these two sets of phenomena and their possible relevance to the mechanism of headache. Further, attempts were made to define specific mechanisms involved in the genesis of these two types of edema.

Submitted for publication June 17, 1955.

Supported by a grant from the U. S. Public Health Service.

From the Study Program in Human Health and the Ecology of Man and the Departments of Medicine (Neurology) and Psychiatry, the New York Hospital-Cornell Medical Center; Commonwealth Fellow in Medicine (Dr. Ostfeld).

LOCAL EDEMA

Observations were made during more than 200 vascular headaches of the migraine type. Significant local alteration of tissue turgor and slight to moderate edema very frequently occurred in the area of headache. While the presence of such local edema was never noted to precede the headache attack, it became more pronounced the longer the headache persisted and often outlasted the headache. In such edematous scalp areas, tenderness and a lowering of deep pain thresholds were predictably noted.[2] The effect of vasoconstrictor agents on the deep pain thresholds and local edema has been described elsewhere.[3] Briefly, when, as a result of administration of vasoconstrictor agents, the intensity of headache subsided, the deep pain thresholds returned to normal levels and edema was reduced. These changes occurred more promptly as a result of administration of vasoconstrictor agents than when the headache ended spontaneously.

Series I

The behavior of the small cranial vessels before and during migraine attacks was visualized in 26 patients by examining the bulbar conjunctival vessels with use of an ophthalmic slit lamp at a magnification of ×47.5.

On six occasions the bulbar conjunctival vessels were examined immediately before a

headache attack. Four times the vessels of the eye on the side on which headache later developed differed in no way from those of the "control" eye on the headache-free side. Twice, however, arteriolar constriction was observed in the eye on the headache side as compared with the "control" eye, with increase in the rhythmic interruption of blood flow (vasomotion).

At the onset of the headache in all 26 patients the arterioles and venules were dilated and the number of visible capillaries was increased on the headache side as compared with the headache-free side. When dilatation was great, a slowing of flow with venular sludging was observed. On five occasions, small hemorrhages were noted along the course of dilated venules. On two occasions, when headache terminated spontaneously, the conjunctival vessels remained dilated and deep pain thresholds of the contiguous scalp areas remained lowered for more than 48 hours. In these patients, when the scalp tenderness was no longer present the eye vessels had returned to their preheadache appearance (Fig. 1). During periods of conjunctival dilatation there was haziness of the conjunctival tissue and an indistinctness of the vascular structures which was compatible with and probably due to local edema. At such times subjects complained of a burning sensation in the eye.

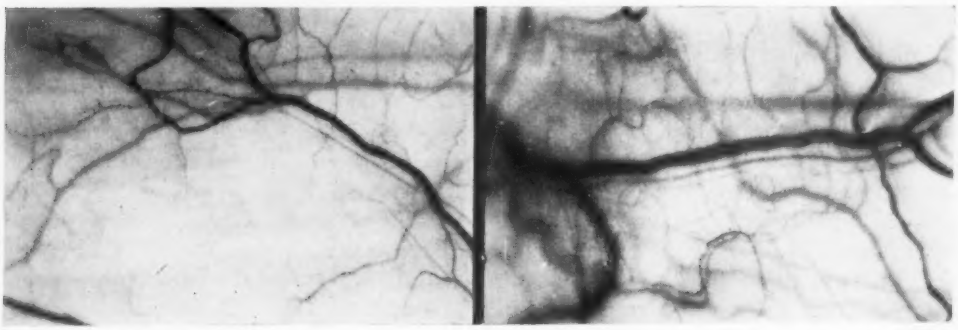


Fig. 1.—Patient S., man aged 29. Photographs of conjunctival vessels during a right-sided attack of migraine headache. Note the dilated conjunctival vessels of the right eye as compared with the nondilated vessels of the left eye.

SERIES II

Arterenol (Nor-epinephrine), 4 cc. of an 0.2% solution in a liter of 5% dextrose in water, was infused intravenously at a rate sufficient to raise systolic B. P. 20 to 30 mm. Hg in this same group of 26 patients during migraine headache attacks. Within a few minutes of the beginning of the infusion of arterenol, arteriolar attenuation with numerous fields exhibiting intermittent cessation of blood flow could be observed. There was, however, at such rates of infusion, no change in the appearance of venules. Usually within 15 to 20 minutes the haziness and blurred outlines attributable to edema began to be reduced, and ultimately they were eliminated. Together with these changes there was a dwindling intensity of headache and reduction of the burning sensation in the eye.

Comment.—Dreisman has recently observed the nail-bed capillaries during intravenous infusion of arterenol.[4] He found that infusion rates sufficient to raise diatolic pressure 10 mm. Hg produced intense capillary narrowing. Redisch and Pelzer[5] microscopically examined the nail-bed capillaries in migraine patients when they were having headaches and observed a blurred appearance of these small vessels. This same blurred appearance could be reproduced during headache-free intervals by inducing overhydration. They further observed that parenteral ergotamine tartrate reduced the degree of blurring and promoted vasoconstriction for

several minutes. Thereafter blurring occurred once again.

The phenomena observed by Redisch and Pelzer can be interpreted as due to local changes in the volume of intracellular and extracellular fluid. Many migraine patients (as will be reported later) retained fluid in the tissues in association with headache. Complaints of the skin feeling thick were common. A local increase of both intracellular and extracellular fluid is suggested as the mechanism responsible for the blurred appearance of capillaries. A vasoconstrictor agent may change intracapillary pressures and rates of flow so as to draw local interstitial and tissue fluid into the circulating blood and, while active, could promote both a narrowing and a clearing of the appearance of capillaries. However, it should be emphasized that the changes in appearance of the conjunctiva and its vessels were entirely distinct phenomena from those seen in the nail beds. The conjunctival edema was predictably associated with local vasodilatation and was terminated by vasoconstrictor agents when headache was eliminated. Furthermore, in contrast to the nail-fold observation, the conjunctival vessels which were dilated during headache and constricted during infusion of arterenol remained constricted after cessation of the infusion.

SERIES III

The sensitivity of vessels of the bulbar conjunctiva on the side of the headache as compared with that on the headache-free side to the topical application of arterenol solutions was ascertained. Sensitivity was assayed by defining that concentration of arterenol in 5% dextrose in water which produced a blanching of capillary beds.

In nine subjects who seldom had headaches the usual range of sensitivity was 1 : 50,000 to 1 : 100,000. In the interval between headaches, in patients subject to migraine attacks, the sensitivity ranged from 1 : 37,500 to 1 : 100,000. At the beginning of a headache attack the sensitivity increased to 1 : 100,000 to 1 : 200,000. During the headache, the sensitivity fell in both bulbar conjunctivae. It fell especially on the side of the headache, with values ranging from 1 : 5000 to 1 : 25,000, and a fall of lesser degree occurred in the contralateral eye, with values varying between 1 : 10,000 and 1 : 50,000. Although the threshold values in headache-free intervals and during headache varied from patient to patient, the fall in sensitivity predictably occurred at the beginning of those headaches in which vasodilatation occurred. These data are schematically shown in Figure 2. Two and a half per cent cortisone ophthalmic suspension was topically applied

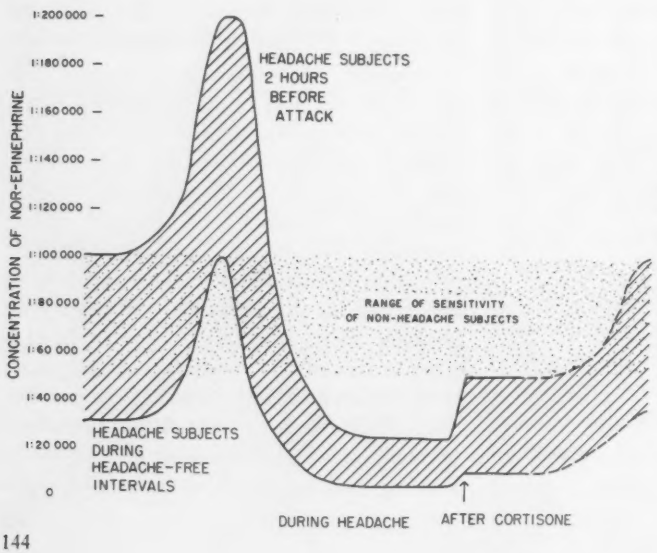


Fig. 2.—Schematic representation of changing sensitivity of conjunctival vessels to arterenol in patients before and during vascular headache attacks. Arrow indicates the change in sensitivity one hour after the topical application of cortisone solution.

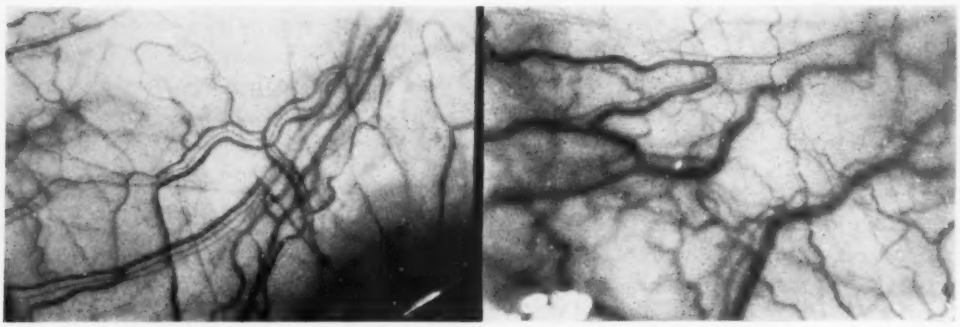


Fig. 3.—Patient W., man aged 29. Photographs of conjunctival vessels during an attack of right-sided atypical facial neuralgia. Note the dilated vessels in the conjunctiva of the right eye.

to the bulbar conjunctiva in an attempt to ascertain whether augmentation of the effect of arterenol as demonstrated by Zweifach in the rat mesoappendix [6] could be reproduced in the vessels of the eye. This agent, while in itself not changing vessel caliber, increased vascular sensitivity to arterenol approximately twofold in both headache and headache-free subjects. Serial observations on two subjects after spontaneous ending of headache attacks revealed that sensitivity to arterenol remained below preattack levels for 48 to 72 hours. Deep pain thresholds of contiguous scalp areas remained lowered for this same period of time.

The bulbar conjunctivae of two patients with atypical facial neuralgia were examined during attacks of pain. There was dilatation of the vascular structures on the side of the pain, as shown in Figure 3. In one of these patients, a concentration of 1 : 5000 arterenol topically applied in the eye on the side of headache was required to blanch capillaries, thus demonstrating a great reduction of threshold sensitivity of the vessels of the bulbar conjunctiva.

Comment.—The resistance of these vessels to vasoconstrictor agents at the time of the headache attacks illuminated the refractoriness of some patients with migraine to the action of such agents. Thus, in order to produce local vasoconstriction suitable for therapeutic effect more agent would be required than would be safe to give. An infusion rate of one drop (0.06 ml.) per second of a 1 : 125,000 dilution of arterenol in 5% dextrose in water usually elevated systolic pressure 20 to 40 mm. Hg. Doubling or trebling the infusion rate resulted in perilous elevations of blood pressure. Even such infusion rates in some instances failed to effect constriction of these dilated vessels.

Another limitation of the efficacy of vasoconstrictor agents in diminishing pain arising from vasodilatation has also become apparent. During many vascular headache attacks, in addition to the characteristic throbbing temporal or frontal headache associated with dilatation of vessels there occurred an aching, less intense, occipital or parietal head pain arising from sustained contraction of skeletal muscle and associated with constriction of nutrient vessels. The administration of such vasoconstrictor agents as arterenol or ergotamine tartrate in eight patients alleviated the throbbing part of the head pain due to the vasodilatation, only to intensify the steady aching pain due to muscle contraction and vasoconstriction. These patients were aware that the pain had moved to a different part of the head and described it as becoming "more a steady ache than a pounding pain." In those patients in whom different portions of the cranial vasculature were behaving differently it is clear that any agent promoting exclusively either constriction or dilatation of blood vessels would be limited in its therapeutic effectiveness.

SERIES IV

Dilatation of conjunctival vessels similar in appearance to that observed in patients having vascular headache of the migraine type was produced experimentally in three subjects by two methods.

1. The local application of soap emulsion in one eye was followed by marked vasodilatation, tears, and pain. In the eye directly irritated by such a chemical means, the dilated arterioles were only one-third to one-half as sensitive to topical arterenol as they were in the unirritated control eye. Local cortisone pretreatment of the irritated eye was associated with a partial restoration of sensitivity to arterenol in two subjects.

2. Vasodilatation of the conjunctival vessels of one eye was produced in three subjects by inhalation of ammonium carbonate through one nostril while both eyes were kept closed to prevent direct stimulation. In this experiment, vasodilatation occurred reflexly as a result of noxious stimulation of afferent fibers in the nasal mucosa. The threshold sensitivity of such dilated arterioles to topical arterenol was reduced by one-third to one-half as compared with those of the control eye. Sensitivity to arterenol following the application of cortisone was partially restored. These results paralleled those seen in chemical irritation and in vascular headache of the migraine type.

Comment.—On the basis of these observations it seemed possible that local dilatation of minute vessels in migraine headache might be due to reflex effects of noxious stimulation from the large and painfully involved arteries. However, on five occasions, observations in patients with severe muscle-contraction headache have revealed unilateral or bilateral constriction of conjunctival vessels. It was more likely therefore that the local dilatation of minute vessels occurred as a part of the migraine attack rather than as a reflex consequence of pain in the head.

SERIES V

An attempt was made to assess the pharmacodynamic effect of tissue juice as relevant to headache. A subject who developed lively urticaria when his skin was exposed to cold was investigated. In this "cold sensitive" subject, the application of an ice bag to the temporal region of the head produced a large urticarial lesion. When erythema and local fluid accumulation appeared, the subject complained of a "disagreeable pounding" sensation in that part of the head. This sensation persisted for 10 minutes, with local redness and swelling remaining for another hour.

Five cubic centimeters of isotonic saline was injected into the wheals produced by this means, and after three minutes 0.1 cc. of fluid was withdrawn and injected into the skin of the subject's forearm. To serve as a control, 5 cc. of isotonic saline was likewise injected subcutaneously in nonurticarial skin and after three minutes 0.1 cc. of fluid was withdrawn and injected into the skin of the opposite forearm. There was a significant lowering of superficial pain thresholds at the site of injection of the fluid withdrawn from the urticarial region for more than an hour. Pain thresholds measured at the site of the control injection were not lowered. Pain thresholds were measured by the Hardy-Wolff-Goodell dolorimeter.

A second series of observations were made on subjects with vascular headache of the migraine type. Isotonic saline was injected into a painful, edematous scalp area and into headache-free scalp areas, and fluid was carefully withdrawn, to avoid contamination with blood. When these fluids were injected into the skin of the forearm, an area of erythema appeared about the site of injection of the fluid from the edematous area. A much smaller zone of erythema was present about the control injection. Also, a slight lowering in pain thresholds of the skin was evident after injection of saline from edematous scalp areas as compared with the thresholds of the skin area with the control injection.

In short, preliminary observations on the properties of this "tissue juice" indicate that it is capable of lowering pain threshold when injected into other tissues. Also, by paper chromatography analyses, such "tissue juice" contains a low-molecular-weight substance infrequently found in the absence of headache. These preliminary observations are now being more systematically pursued.

Comment.—On the basis of the foregoing data, the following mechanism of local edema formation and local tissue tenderness was postulated. Dilatation of arterioles accompanied by opening of precapillary sphincters effectively raised intracapillary hydrostatic pressure, while capillary osmotic pressure remained constant. The intracapillary pressure shift favored the transudation of water and chemical constituents of plasma into the surrounding tissue. The local tissue tenderness and other evidences of tissue damage were presumed to be due to the presence in such local fluid accumulations of a substance or substances which had the capacity to produce tissue alterations and thus lower pain thresholds.* Such lowering of pain thresholds intensifies the pain due to dilatation of the larger arteries. Vasoconstrictor agents by constricting arterioles and arteries were effective in returning the local intravascular pressure relationships toward normal, favoring reabsorption of water and other chemical substances into the circulating plasma.

WIDESPREAD FLUID RETENTION

The phenomenon of widespread fluid retention was studied in 134 patients with vascular headache of the migraine type. The reported data were obtained from history and examination; daily weight records were taken on 51 patients, and more detailed observations were made on smaller groups. The clinical manifestations of the widespread fluid retention were complaints about the sudden gain in weight, "tightness of rings on fingers," "rings cannot be pulled off," "shoe laces or shoes are uncomfortable," belts are "too tight," girdles and brassières "feel too snug," "clothes don't fit." The subjects even complained that the skin "feels thicker." This variety of edema, in contrast to the localized edema in the region of the headache, was nontender. These phenomena usually reached their maximum just before the onset of headache.

Sixty-three of the 134 patients affirmed that they had experienced one or more of the above symptoms in association with headache. Daily weight measurements were made by 51 of these patients through at least one headache attack. In 31 there was a gain of approximately 2 lb.; 16 gained 3 to 5 lb., and a weight gain of 17 lb. was noted in one subject. Six subjects who weighed themselves twice daily observed that the weight gain was manifested before the onset of headache by periods ranging from four hours to six days.

The time of occurrence of diuresis was less predictable. It commonly occurred during the periods of dwindling headache intensity, but it was also observed before or immediately after the onset of the headache. Less frequently, two and in one case even three headaches were experienced and terminated during a period of sustained weight gain, with diuresis occurring only on elimination of the second or third headache.

Studies were undertaken to ascertain the relevance of this generalized fluid retention to the genesis, frequency, and severity of headache.

SERIES I

On four occasions, three patients subject to the migraine type of vascular headache were observed during a period of weight gain. When these patients, because of various premonitory head sensations, were anticipating headaches, they were given 1 to 2 cc. of a mercurial diuretic (mercaptomerin [Thi-

* It has been previously demonstrated that blister fluid injected intradermally resulted in a lowering of pain threshold in the skin of the upper arm, whereas in a contralateral skin area similarly injected with isotonic saline, pain thresholds were not lowered (Bigelow, N. H.; Harrison, I. R.; Goodell, H., and Wolff, H. G.: Unpublished data).

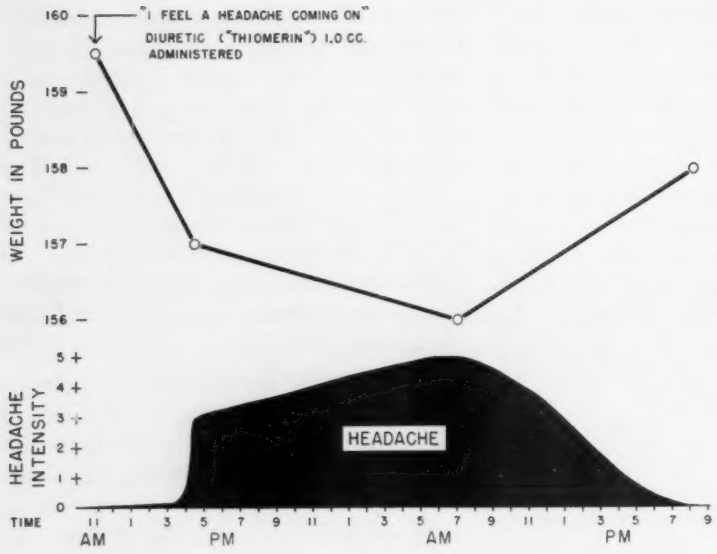


Fig. 4.—Failure of induced diuresis to prevent a migraine headache attack.

omerin] or meralluride, U. S. P. [Mercuhydrin]). A diuresis was produced on three of the four occasions, but the usual vascular headache in each instance began at the anticipated time. On two occasions the headache began during the induced diuresis, and once, three hours later. The intensity and duration of pain were about the same as in previous attacks. A typical instance of the failure of induced diuresis to prevent headache is shown in Figure 4.

SERIES II

Various agents were used to prevent fluid accumulation, and the effect on the frequency and intensity of headache was noted. Three patients were studied in the following manner. Daily body weight and occurrence and intensity of headache in each patient were recorded for one month, during which time no diuretics were taken. Acetazoleamide (Diamox), a carbonic anhydrase inhibitor type of diuretic, was then given in amounts of 250 mg. orally twice daily for another

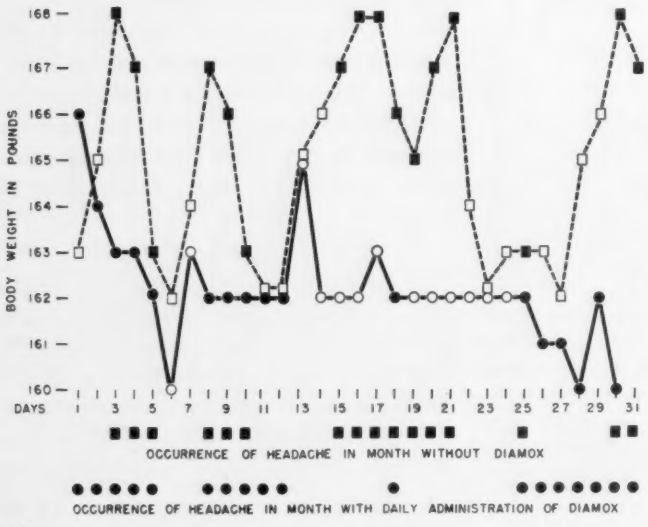


Fig. 5.—Occurrence of headache with and without induced diuresis.

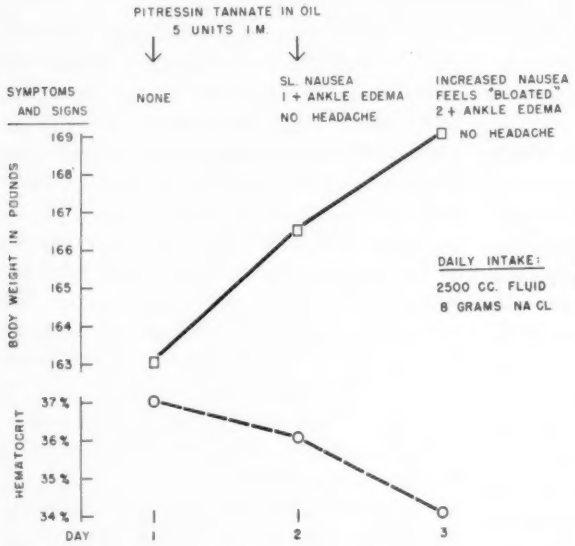


Fig. 6.—Failure of induced hydration to precipitate headache.

month to each of the three patients. Again, the body weight each day and the incidence and severity of headache were recorded. During the administration of the diuretic agent weight fluctuations were minimized but the frequency and severity of headache were not altered, as shown in Figure 5. Also, two subjects were given a low-salt (approximately 2 gm. daily) diet for two weeks and two were given sodium-removing carboresins for one to two weeks. During the low-salt regimen the variations in body weight were not strikingly altered and headache incidence and severity was unchanged as compared with the control period.

Series III

Attempts to precipitate headache by inducing a state of overhydration through the use of hormones were made. Three patients subject to the migraine type of vascular headache were given daily injections of 5 units of vasopressin (Pitressin) tannate in oil and drank 2500 cc. of fluid daily for two to three days. A weight gain of as much as 9 lb. was effected, accompanied by nausea, abdominal cramps, and malaise, but no headache resulted (Fig. 6). Likewise, in two patients, the injection of 20 mg. desoxycorticosterone acetate (DOCA) i. m. and the ingestion of 20 gm. salt daily were attended with moderate weight gain but no headache was experienced.

Comment.—The foregoing data indicate that weight gain and widespread fluid retention are phenomena which are concomitant but not causally related to headache, since (1) weight gain did not invariably occur with headache; (2) weight gain was prevented without preventing the occurrence or altering the severity of headache in subject to migraine headache; (3) weight gain was induced without inducing headache in patients subject to them.

Series IV

In order to examine more closely the changes in urinary excretion of corticosteroids, sodium, potassium, and water occurring in association with migraine, urine was collected and records of headache kept on nine patients for periods of from two to six days. Patients were instructed to maintain their intake of food, salt, and fluid as nearly consistent as possible, beginning three days before the anticipated time of headache and continuing throughout the collection period. Analysis of intake reports indicated that an approximate constancy of diet was maintained. Patients were performing their usual work during the collection period. The daily outputs of urine were collected in four com-

bined specimens, as follows: (1) 8 to 12 a. m.; (2) 12 to 4 p. m.; (3) 4 to 8 p. m., and (4) 8 p. m. to 8 a. m. Sodium and potassium concentrations were ascertained in duplicate by means of a Barclay flame photometer. Corticoid concentration was ascertained in duplicate aliquots by the method of Glenn and Nelson.[7] Standard hydrocortisone solutions were analysed in duplicate specimens with each assay, and recoveries ranged consistently between 74% and 88%. Creatine concentrations were ascertained by means of the method of Bonsnes and Taussky [8] as a check on the accuracy of collection of urine specimens.

There was no consistent and predictable pattern in the excretion of sodium, potassium, water, and corticosteroids, in association with headache. Usually the excretion rates of all these substances rose and fell together. During those headaches preceded by weight gain, there was usually a reduction of excretion of all, followed by a diuresis of all as the headache was dwindling in intensity. In those headaches not associated with weight gain there was no significant variation in the excretion rates of any of these substances.

Comment. — It is conceivable that the general fluid retention might augment the local tissue edema at the site of headache, thus intensifying the pain. Wasserman, Loeb, and Mayerson [9] have shown that increases in blood volume of 10% or more lead to an increase in capillary permeability to large molecules. Although observations in patients with vascular headache have indicated that blood volume increase of this magnitude would be a rarity in a migraine attack, it may be that, in a few cases, diffusion into the site of head pain of larger plasma molecules could be abetted by such hypervolemia and that headache intensity would thereby be augmented.

It is likely that the alteration in retention and excretion of sodium, potassium, water, and corticosteroids is not causally related to headache but is part of a nonspecific alteration of fluid metabolism and urinary excretion which may accompany vascular headache.

Series V

Three subjects were examined daily for periods of 5 to 14 days. Careful observations and notes were made on the occurrence and severity of headache, weight gain, life situa-

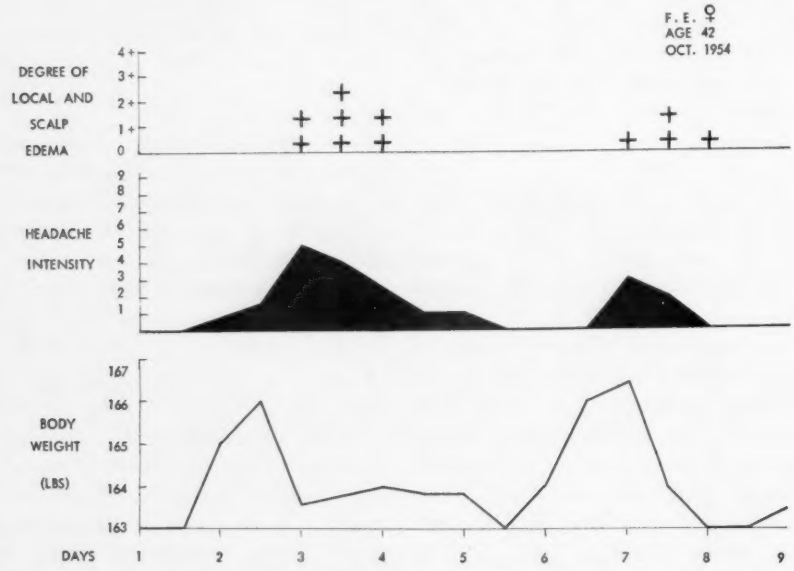


Fig. 7.—Note the disparity in time between the occurrence of local edema and general accumulation of fluid.

tions, feelings, and behavior patterns. It was revealed that weight gain occurred in these subjects on days when they perceived their life situation as threatening, to which they responded with increased attention, conscientiousness, alertness, and physical activity. This behavior pattern was accompanied by feelings described by patients as being "on edge" or "tense." The diuresis and, indeed, the onset of headache when it occured commonly took place within a period of subsequent "let down" or "relaxation."

Comment.—Schottstaedt and Wolff [1] have shown that this behavior pattern in response to situations perceived as threatening is accompanied by a reduced urinary excretion of sodium, potassium, and water and is followed by a diuresis of all these substances during subsequent relaxation. The occurrence of headache in those subject to them in such a setting has also been well documented. It is likely therefore that headache and overhydration are consequences of parallel body dysfunctions which occur independently as parts of a response to a threatening life situation. The mechanism of the generalized fluid retention remains unclear.

Series VI

In order to demonstrate further the nonrelationship between the nonlocalized edema and localized edema, daily observations on both were made on three subjects. Alteration in body weight was taken as an index of widespread fluid retention and edema. The degree of scalp edema was taken as an index of localized edema and was readily estimated from the depth of depression remaining after a standard measured pressure had been applied to the relevant area of the scalp. Two of the patients showed local scalp edema during three headache episodes without appreciable changes in body weight. The third subject, observed during two headaches, experienced successively gain in weight, diuresis with loss of weight, and then local scalp edema. When body weight was maximal, local scalp edema had not yet occurred, and when local scalp edema was most notable diuresis had already lowered body weight to its initial level (Fig. 7). It is therefore evident that these two phenomena are separated in time and result from the operation of different mechanisms.

Summary and Conclusions

Visualization of bulbar conjunctival vessels of patients during attacks of vascular headache of the migraine type by means of an ophthalmic slit-lamp revealed (*a*) vasoconstriction preceding (inconstantly observed) and (*b*) vasodilation (nearly constantly observed) with evidence of edema and sometimes hemorrhage during the migraine attack. Vasoconstriction with clearing of localized edema followed the intravenous infusion of dilute arterenol solution as the headache diminished in intensity.

The sensitivity of minute vessels in the bulbar conjunctiva to the vasoconstricting agent arterenol was increased at the onset of headache and was greatly reduced during the headache attack.

The local edema at the headache site in subjects during vascular headache of the migraine type occurred as an accompaniment of the local vasodilatation. It was predictably associated with a lowering of deep pain thresholds. Evidence suggests that there was in such local fluid accumulation a substance or substances which damaged tissue, lowered deep pain thresholds, and hence made the previously described dilatation of large arteries during such headache more painful. The local fluid accumulation was therefore highly pertinent to the mechanism of headache.

The nonlocalized edema that occurred in those subject to migraine headache was often but not invariably coincident with the headache. It commonly appeared during periods of increased alertness and driving activity, could be induced in patients subject to migraine attacks without inducing headache, and could be abolished without preventing headache. It was therefore neither causally nor mechanically related to the mechanism of the headache.

REFERENCES

1. Schottstaedt, W. W., and Wolff, H. G.: Variations in Fluid and Electolyte Excretion in Association with Vascular Headache of the Migraine Type, A. M. A. Arch. Neurol. & Psychiat. **73**:158, 1955.

2. Wolff, H. G.; Hunis, M. M., and Goodell, H.: Evidence of Tissue Damage and Changes in Pain Sensitivity in Subjects with Vascular Headaches of the Migraine Type, A. M. A. Arch. Int. Med. **92**:478, 1953.

3. Ostfeld, A. M., and Wolff, H. G.: Nor-Epinephrine and the Mechanism of Vascular Headache of the Migraine Type, A. M. A. Arch. Neurol. & Psychiat., to be published.

4. Dreisman, S. E.: The Reaction of the Capillary Bed of the Nailfold to the Continuous Intravenous Infusion of Levo-Nor-Epinephrine in Patients with Normal Blood Pressure and with Essential Hypertension, J. Clin. Invest. **33**:975, 1954.

5. Redisch, W., and Pelzer, R. H.: Capillary Studies in Migraine: Effect of Ergotamine Tartrate and Water Diuresis, Am. Heart J. **26**:598, 1943.

6. Zweifach, B. W., and Metz., D. B.: Relation of Blood-Borne Agents Acting on Mesenteric Vascular Bed to General Circulatory Reactions, J. Clin. Invest. **34**:653, 1955.

7. Glenn, E. M., and Nelson, D. H.: Chemical Method for the Determination of 17-Hydroxycorticosteroids and 17-Ketosteroids in Urine Following Hydrolysis with Beta-Glucuronidase, J. Clin. Endocrinol. **13**:911, 1953.

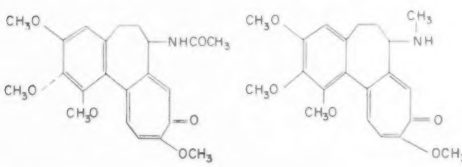
8. Bonsnes, R., and Taussky, H.: On the Colorimetric Determination of Creatinine by the Jaffe Reaction, J. Biol. Chem. **158**:581, 1945.

9. Wasserman, K.; Loeb, L., and Mayerson, H. S.: Permeability of Capillaries to Large Molecules, Fed. Proc. **14**:159, 1955.

The Effect of Intravenous Demecolcine (Colcemid) on Acute Gout

WILLIAM C. KUZELL, M.D.
RALPH W. SCHAFFARZICK, M.D.
and
W. EDWARD NAUGLER, M.D., San Francisco

In 1950 Šantavý and Reichstein [1] reported the isolation of several previously unknown alkaloids from the meadow saffron (Colchicum autumnale), the source of colchicine. Subsequently the pharmacological properties of these alkaloids were investigated by Schär, Loustalot, and Gross,[2] and one of the compounds, demecolcine, was found to have an antimitotic effect equivalent to that of colchicine in fibroblast cultures and considerably less toxicity in laboratory animals. Structurally, demecolcine differs from colchicine in the replacement of the acetyl group at the nitrogen by a methyl radical (Fig.).



Formulas of colchicine (left) and demecolcine (desacetylmethylcolcine) (right).

Extensive laboratory study by Schär, Loustalot, and Gross demonstrated that, in all animal species, demecolcine is considerably less toxic than colchicine. In mice, for example, the intravenous lethal dose of demecolcine is as much as 40 times greater than that of colchicine. Paradoxically, in mice demecolcine is about six times more toxic orally than intravenously whereas with colchicine intravenous administration is more toxic than oral administration. In normally developing embryonic chick osteoblasts, demecolcine and colchicine were shown to interrupt mitosis in the metaphase essentially in the same manner. To inhibit mitosis in a variety of animal and human tumor tissue cultures, demecolcine was generally effective only in concentrations greater than those adequate for antimitotic activity in normal tissues. When given daily to rabbits, demecolcine produced a marked diminution of circulating leucocytes and a destruction of cells in lymph nodes. Repeated daily doses of demecolcine in mice resulted in severe impairment of spermatogenesis and, to a lesser degree, of ovarian function. After large single doses in mice, demecolcine caused inhibition of mitosis and necrotic changes in intestinal villi. The margin between generally toxic doses and those inhibiting the growth of certain transplantable tumors in animals was found to be more favorable for demecolcine than for colchicine.

Clinically demecolcine has been tested in the treatment of a variety of neoplastic disorders. Moeschlin, Meyer, and Lichtman [3] reported in 1953 that the alkaloid, with an almost selective effect on granulocytes in

Submitted for publication May 19, 1955.

Dr. Richard Roberts, of Ciba Pharmaceutical Products, Inc., made available the Colcemid used in these studies.

From the Rheumatic Disease Study Group, Department of Pharmacology and Therapeutics, Stanford University School of Medicine.

Effect of Introvenous Demecolcine on Acute Gout

Patient	Sex	Age, Yr.	Known Duration of Gout, Yr.	Serum Uric Acid, Mg./100 Cc.	Demecolcine, I. V.			Side-Effects	Therapeutic Response	Remarks
					Dose, Mg.	Doses, No.	Period, Days			
1. B. G.	M	43	13	8.7	3	2	2	0	Good	.....
2. G. K.	M	50	2	2.6	2	1	1	0	Good	On probenecid
3. E. W.	M	42	6	7.0	2	2	2	Diarrhea	Good	.....
4. D. J.	F	57	2	9.0	2	1	1	0	Good	.....
5. E. W.	M	70	1	4.6	2	2	2	0	Good	On probenecid
6. M. B.	M	56	6	8.0	3	1	1	0	Good	.....
7. E. C.	M	44	10	7.8	2	1	1	0	Good	.....
8. M. T.	F	70	8	8.5	2	2	2	Diarrhea	Good	Phlebitis from i. v. colchicine
9. C. R. B.	M	75	45	9.8	1 to 4	15	4 mo.	0	Good	Phlebitis from i. v. colchicine
10. A. S.	M	70	35	10.5	2	4	8	0	Fair	Postoperative
11. C. C.	M	53	15	...	3	1	1	0	Good	.....
12. G. N.	M	77	42	11.9	2	1	1	0	Good	.....
13. A. P.	M	44	1	7.8	3	2	2	0	Fair	.....
14. L. C.	M	54	15	6.8	2	1	1	0	Poor	.....
15. R. S.	F	64	20	4.9	2	2	2	0	Fair	.....
16. G. C.	M	53	10	...	3	1	1	0	Fair	Postoperative
17. H. S.	M	83	11	9.5	3	1	1	0	Good	.....
18. R. S.	M	46	10	6.7	1	2	7	0	Good	.....
19. D. V.	M	69	12	8.4	1	1	1	0	Good	.....
20. J. F.	M	55	25	10.6	3	2	2	0	Good	.....

experimental animals, was effective as continuous oral therapy in three patients with chronic myeloid leukemia. No benefit was obtained in other malignant diseases such as myeloma, lymphosarcoma, Hodgkin's disease, and sarcoma. Demecolcine appeared to stimulate a fatal exacerbation in a patient with lymphatic leukemia, and the authors warn emphatically against the application of the alkaloid in this disease. Undesirable side-actions otherwise were not striking. There were no gastrointestinal disturbances. It was noted, however, that, as with other cytostatics, inhibition of spermatogenesis and ovulation should be expected. Bock and Gross [5] reported mild pruritus and depilation in 4 of 20 patients who were receiving demecolcine in daily doses up to 20 mg. orally or 16 mg. intravenously.

Leonard and Wilkinson [4] have also recently reported that desacetylmethylcolchicine (Colcemid) is of "greatest value in chronic myeloid leukemia, having a distinct depressant action on the granulocytes and producing rapid reduction of splenomegaly and a marked clinical improvement in 6 of 8 such treated cases."

To our knowledge there has been no report concerning the use of demecolcine in the treatment of acute gout. It is the purpose of this communication to describe our experience with the alkaloid in such cases. Although demecolcine is available in both tablet and solution preparations, our clinical trials in gout have dealt primarily with intravenous therapy. The efficacy of intravenous colchicine in gout and in acute sensitivity states has been established.[6] In our study no attempt was made to compare the therapeutic effectiveness of colchicine and demecolcine but simply to establish whether or not the new alkaloid possessed activity against acute gout. The results of this investigation are summarized in the Table.

Of the 20 patients, 17 were men and 3 were postmenopausal women. The group ranged in age from 42 to 83 years, and the known duration of gout, from 1 to 45 years. In patients showing normal serum uric acid levels, tophi confirmed the clinical impression of gout. Only acute attacks of the disorder were treated. Duration of these exacerbations before treatment ranged from 1 to 30 days. Daily intravenous dosage was 1 to 4 mg. (considerably less than that given by Bock and Gross for more desperate disorders). In 18 patients only 2 injections were given; in 1 man 4 injections were given, and in the other (C. R. B.) during a four-month period, a total of 15 doses for repeated attacks.

Therapeutic response was graded as "good" if complete remission of the acute gout attack was effected within 48 hours. If only partial amelioration of signs and symptoms was achieved, the response was graded as "fair," and if no improvement was noted the response was called "poor." According to these criteria, 15 of the patients had a good; 4, a fair, and 1, a poor result. This last patient, a 64-year-old woman, has never been found to have an elevated serum uric acid level but has numerous large tophi.

Despite the absence of gastrointestinal irritation in the patients of other investigators, two of our patients suffered diarrhea after the injection of 2 mg. demecolcine on two consecutive days. No other undesirable side-action was detected. Notably lacking was venous irritation. In previous trials with intravenous colchicine we had encountered five cases of severe phlebitis, characterized by exquisite tenderness and hyperemia retrograde to the site of injection and persisting for as long as three weeks. No such reaction followed the intravenous administration of demecolcine.

SUMMARY

Demecolcine (Colcemid), an alkaloid from the meadow saffron, differing from colchicine structurally in the replacement of the acetyl by a methyl radical, was given intravenously to a series of 20 patients with acute gout. Of the 20 patients, 15 enjoyed complete remission within 48 hours after the administration of 1 to 4 mg. of demecolcine. Four other subjects were afforded partial amelioration of signs and symptoms. The only undesirable side-action was the occurrence of diarrhea in 2 of the 20 patients.

REFERENCES

1. von Uffer, A.; Schindler, O.; Šantavý, F., and Reichstein, T.: Teilsynthese des Demecolcins und einiger anderer Colchicinderivate, Helvet. chim. acta **37**:18, 1954.

2. Schär, B.; Loustalot, P., and Gross, F.: Demecolcin (Substanz F), ein neues, aus Colchicum autumnale isoliertes Alkaloid mit starker antimitotischer Wirkung, Klin. Wchnschr. **32**:49-57, 1954.

3. Moeschlin, S.; Meyer, H., and Lichtman, A.: Ein neues Colchicumnebenalkaloid (Demecolcin Ciba) als Zytostatikum myeloischer Leukämien, Schweiz. med. Wchnschr. **83**:990, 1953.

4. Leonard, B. J., and Wilkinson, J. F.: Desacetylmethylcolchicine in Treatment of Myeloid Leukaemia, Brit. M. J. **1**:874, 1955.

5. Bock, H. E., and Gross, R.: Colchicinwirkungen und Granulocytopoese: Klinische und experimentelle Beobachtungen mit Substanz F aus Colchicum autumnale, Klin. Wchnschr. **31**:816, 1953.

6. Davis, J. S., Jr., and Bartfeld, H.: Effect of Intravenous Colchicine on Acute Gout, Am. J. Med. **16**:218, 1954.

7. Mugler, A.: Action de la colchicine sur les accidents allergiques, Ann. méd. **51**:495, 1950.

The Diagnosis of Bronchogenic Carcinoma in Patients with Pulmonary Tuberculosis

MORTON E. SHAFRAN, M.D., Chincoteague, Va.
and
JULIUS KAVEE, M.D., New York

The coexistence of pulmonary tuberculosis and carcinoma of the lung was reported infrequently prior to 1940,[1] and rarely were these two diseases diagnosed simultaneously before death. Cooper,[2] in an exhaustive study of the literature prior to 1932, found only 45 cases of combined tuberculosis and carcinoma of the lung. During the last two decades, there has been a rapid rise in the incidence of bronchial carcinoma so that these tumors are now the most frequent form of malignant disease causing death among adult males. During the same period, there has been a shift in the age incidence of patients with pulmonary tuberculosis so that an even greater percentage are now found alive beyond the age of 40. The use of antituberculous chemotherapy and pulmonary resections will probably further increase the number of tuberculous patients surviving to an age where cancers are not uncommon.

In the past 20 years, a total of 114 cases of primary lung cancer were reported among 7847 autopsies on male and female patients of all ages with tuberculosis.* This is an over-all incidence of 1.45% of pulmonary carcinoma among tuberculous adults. The incidence of bronchogenic carcinoma among tuberculous men over 40 years of age is undoubtedly much higher than in the entire tuberculous population, since such carcinomas are rarely found in younger males and are less common, though not uncommon, in females.

During a 12-month period at Montefiore Hospital, the antemortem diagnosis of coexisting bronchogenic carcinoma and pulmonary tuberculosis was made and confirmed in six patients, all of whom were men past the age of 40. During this period, 73 male patients over the age of 40 with pulmonary tuberculosis were admitted to the pulmonary service. This is an incidence of 8.2% of coexisting pulmonary tuberculosis with bronchogenic carcinoma among men past 40 years of age. Although this does not necessarily indicate the true coincidence of these diseases, it suggests a current rise in the frequency with which the diagnosis of bronchogenic carcinoma is being made among tuberculous men over 40 years of age.

These patients with coexisting pulmonary tuberculosis and bronchogenic carcinoma present a diagnostic challenge, since the differential diagnosis of these two diseases may be extremely difficult and the presence of both can multiply these difficulties. Tuberculous patients who are under close clinical and frequent roentgenological observation in hospitals, santoria, and clinics also present a golden opportunity for the early diagnosis of bronchogenic carcinoma, since serial chest x-rays present the earliest opportunity to detect primary lung tumors.

Submitted for publication May 20, 1955.

Fellow of the American Trudeau Society, 1953-1954 (Dr. Shafran); from the Division of Pulmonary Diseases, Montefiore Hospital (Dr. Kavee).

* References 3-8.

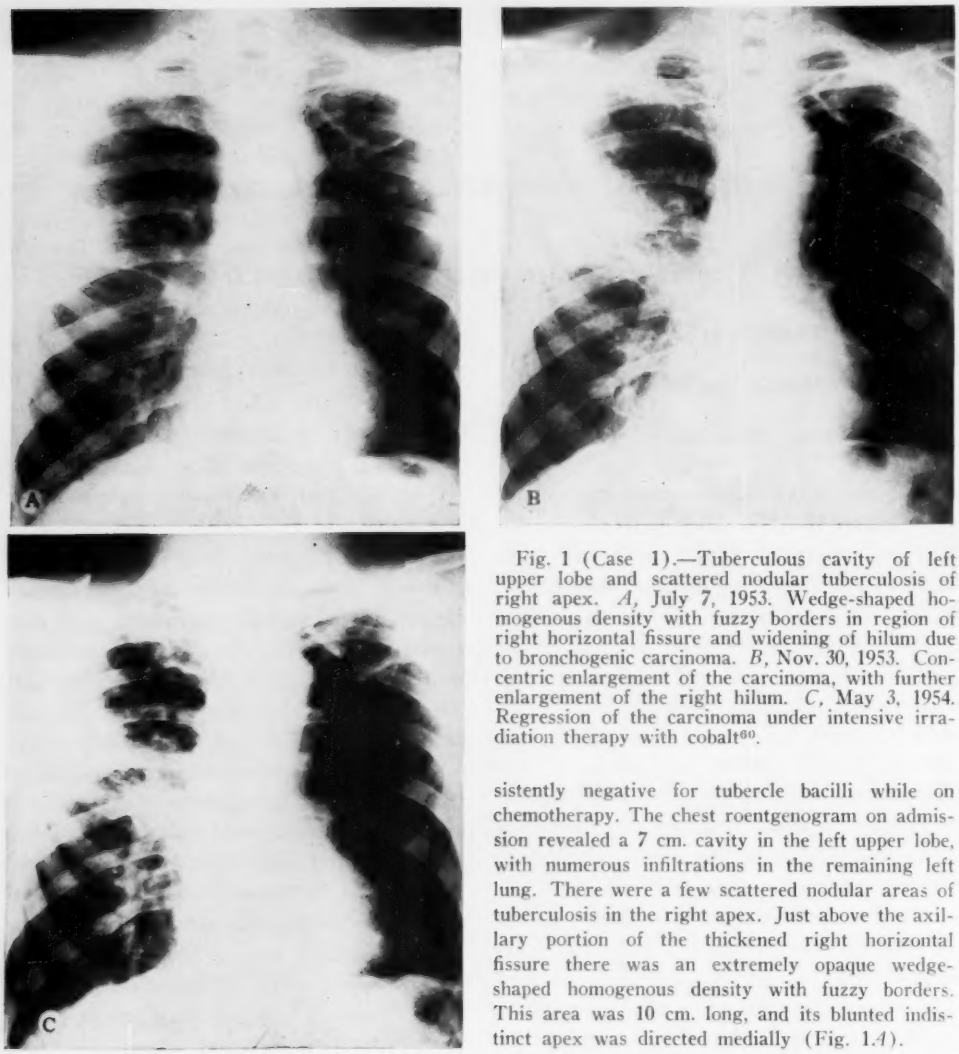


Fig. 1 (Case 1).—Tuberculous cavity of left upper lobe and scattered nodular tuberculosis of right apex. *A*, July 7, 1953. Wedge-shaped homogenous density with fuzzy borders in region of right horizontal fissure and widening of hilum due to bronchogenic carcinoma. *B*, Nov. 30, 1953. Concentric enlargement of the carcinoma, with further enlargement of the right hilum. *C*, May 3, 1954. Regression of the carcinoma under intensive irradiation therapy with cobalt^{60}.

REPORT OF CASES

CASE 1.—H. Y., a 56-year-old man, was admitted to the hospital on May 30, 1953. For two years he had coughed and noted increasing exertional dyspnea. In November, 1952, he had hemoptysis and fever. At this time an x-ray revealed a pulmonary cavity, and two sputum cultures were positive for tubercle bacilli. From February to May, 1953, he had received streptomycin and isoniazid.

On admission, he was afebrile and appeared to be well nourished. The initial examination revealed no abnormalities except for slight clubbing of the fingers and moist rales with diminished breath sounds throughout the left chest and over the right chest anteriorly. The sputum cultures were consistently negative for tubercle bacilli while on chemotherapy. The chest roentgenogram on admission revealed a 7 cm. cavity in the left upper lobe, with numerous infiltrations in the remaining left lung. There were a few scattered nodular areas of tuberculosis in the right apex. Just above the axillary portion of the thickened right horizontal fissure there was an extremely opaque wedge-shaped homogenous density with fuzzy borders. This area was 10 cm. long, and its blunted indistinct apex was directed medially (Fig. 1*A*).

On June 6, 1953, streptomycin, *p*-aminosalicylic acid, and isoniazid were started again. The tuberculosis on the left regressed, the sputum remained negative, and the patient continued to feel well. However, the wedge-shaped area on the right grew rapidly and became more opaque (Fig. 1*B*). Bronchoscopy in June, 1953, failed to reveal any abnormality, and the bronchial washings did not contain abnormal tissues or cells on histological examination. Two needle biopsies of the mass failed to obtain abnormal cells, but a third, in October, 1953, resulted in the demonstration of malignant cells. A second bronchoscopy at this time visualized a mass in the right upper lobe bronchus which proved to be due to a squamous-cell carcinoma. Resection of the tumor at this time would have involved a pneumonectomy in the presence of extensive active

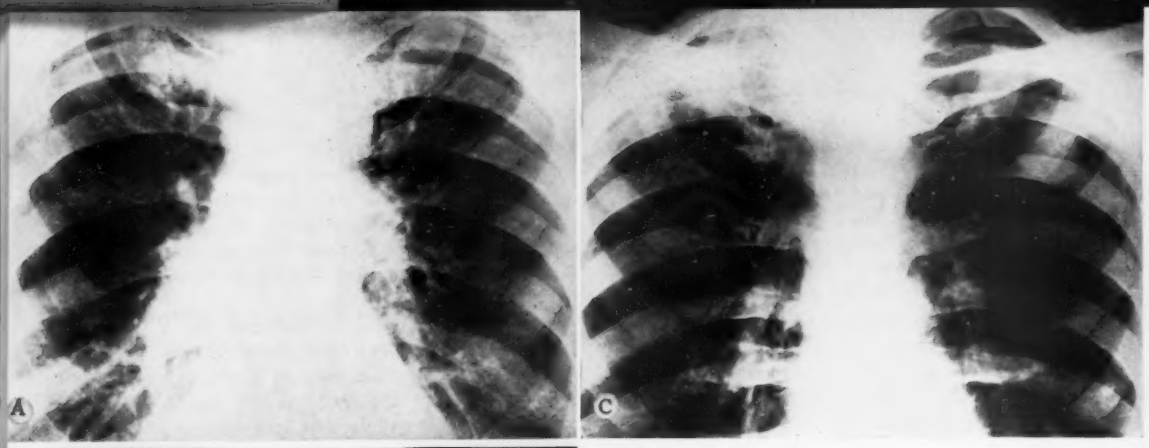


Fig. 2 (Case 3).—Stable bilateral nodular tuberculosis of both upper lobes of many years' duration, with serial roentgen observation at the Westchester Division since April, 1952. *A*, Sept. 7, 1953. First appearance of linear nodular opacity of carcinoma at level of first interspace anterior. *B*, Jan. 11, 1954. Amorphous shadow of growing carcinoma in same locale. *C*, Feb. 3, 1954. Carcinoma now visualized as larger denser round shadow with fuzzy circumference.

contralateral pulmonary tuberculosis. This was deemed inadvisable, and the patient was given 5500r with radioactive cobalt therapy to the tumor, with regression of the mass on x-ray (Fig. 1*C*).

Comment.—The provisional diagnosis of bronchogenic carcinoma was based primarily on the x-ray appearance of the density in the right lung and its progression in spite of active antituberculous therapy.

Case 2.—H. D., a 49-year-old man, was admitted to the hospital on Dec. 24, 1953, with a history of an intermittent productive cough of 10 years' duration, which he ascribed to heavy cigarette smoking over the past 30 years. In 1951 he had had a hemoptysis of about 50 cc. In the past three months he had noted anorexia with an associated weight loss of 8 lb. He had felt spells of weakness and nervousness accompanied by cold sweats whenever he failed to eat on time. He suggested that, since these feelings were relieved by food, he might have a low blood sugar. He was referred to the tuberculosis service with tubercle bacilli in his sputum and a chest film thought to represent pulmonary tuberculosis.

He appeared emaciated and chronically ill. Small firm lymph nodes were felt in both anterior and posterior cervical regions. The breath sounds and tactile fremitus were diminished over the left upper lung field, and inspiratory rales were present there. There was pronounced clubbing of the fingers and toes. The systolic blood pressure was 110 and the diastolic was 65 mm. of mercury. The sputum was found to contain tubercle bacilli on culture on two occasions. The fasting blood glucose was 61 mg. per 100 cc. The initial chest roentgenogram revealed a fibronodular infiltration occupying the upper third of the right lung. On the left side in the apex there was a dense ovoid homogenous opacity, 3.5×3 cm., with a fuzzy circumference, reaching down to the level of the fourth interspace posteriorly. On lateral view this area seemed to be in the apex of the left lower lobe. The upper portion of the left hilum seemed moderately enlarged, with fine linear streaks directed toward the apical density. Bronchoscopy did not reveal any endobronchial abnormalities. The sputum and bronchial washings were negative for tumor cells. The patient was given five weeks of treatment with streptomycin, *p*-aminosalcylic acid, and isoniazid without appreciable change in the left lung. In February, 1954, a biopsy of the supraclavicular and cervical glands failed to reveal any abnormality. However, the left scalenus fat pad, which was also removed, contained three small nodes with anaplastic metastic carcinoma.

Two weeks after the biopsy, while awaiting x-ray irradiation therapy, the patient suddenly complained of severe upper anterior chest pain radiating to the neck and back. His temperature rose to 102.5 F, and he went into shock with cyanosis, sweating, and faint pulse. The systolic pressure was below 60 mm. Hg. The heart sounds were almost inaudible. The electrocardiogram revealed a low voltage of the main ventricular deflection in all leads. The

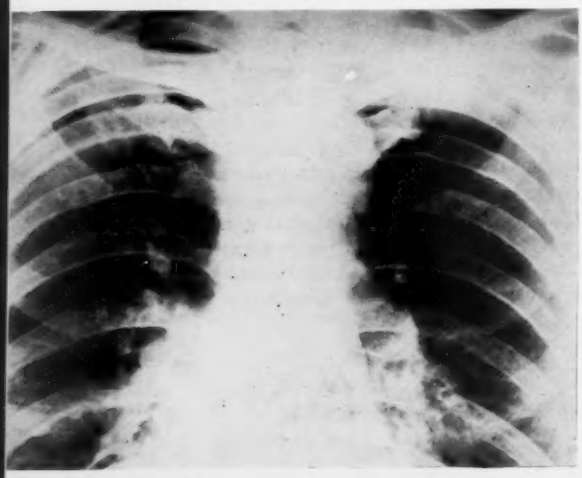
T-wave was inverted in Lead aV_L, and there were high T-waves in leads II, III, and aV_F. The ST-segments of Leads V_3 and V_4 were elevated. The serum Na was 119 mEq., and the K was 7.7 mEq. Despite arterenol, whole blood, saline, and dextrose solutions intravenously and desoxycorticosterone, he died within 24 hours of the start of this episode.

Postmortem examination revealed an adenocarcinoma of the apex of the left lower lobe with metastases to the epicardium and pericardium, which contained a hemorrhagic effusion. Both adrenal cortices were completely replaced by neoplasm. There was fibrocaseous tuberculosis of the right upper lobe, the left lower lobe, and the left hilar glands.

Comment.—There was roentgen evidence of fibrocaseous tuberculosis and a sputum positive for tubercle bacilli. Diagnosis of bronchogenic carcinoma was based largely on the roentgen pattern of the left lung and the failure of antituberculous therapy to affect the disease in the left lung favorably. The clubbing of the fingers and emaciation were also suggestive of a bronchogenic malignant disease.

CASE 3.—E. R., a 69-year-old male sanatorium employee, was admitted to the hospital on Dec. 18, 1953. He had had a chronic cough productive of a small amount of sputum for many years. He had had one episode of blood-streaked expectoration in 1952 but had felt well and was continuously employed. He had worked in the hospital sanatorium since 1952, and routine chest x-ray films taken there had revealed symmetrical scattered nodular infiltrations in both upper lobes. The x-ray film of Sept. 7, 1952, revealed a new linear, somewhat nodular, infiltration about 2 cm. long and 2 mm. wide, paralleling the middle of the lower anterior border of the left first rib (Fig. 2*A*). Serial films demonstrated a gradual growth of this linear infiltration so that by August, 1953, it had become triangular in shape, sharply defined, and extremely opaque and measured 2 by 1.5 cm. (Fig. 2*B*). At this time he once more had a slight episode of blood streaking. It was felt that he might have a peripheral carcinoma of the lung, and he was admitted to the ward for investigation.

Fig. 3 (Case 4).—Fibroid tuberculosis of right upper lobe. Large dense ovoid shadow in left apex. Thoracotomy revealed squamous-cell carcinoma of left upper lobe with invasion of the thoracic wall.



An admission physical examination was essentially normal. The sputum and gastric cultures were consistently negative for acid-fast bacilli. Bronchoscopy revealed no abnormalities. No tumor cells were found in the sputum or bronchial washings. The patient was placed on bed rest, streptomycin, and *p*-aminosalicylic acid therapy for six weeks, without roentgenological change of the expanding lesion in the left lung.

On Feb. 8, 1954, the left upper lobe, containing an anaplastic carcinoma, was resected. The pleura and the mediastinum were free of evident metastases. He made an uneventful recovery from the operation. Although the tuberculosis did not progress, three months postoperatively the carcinoma had spread into the remaining left lung and mediastinum.

Comment.—The patient was known to have pulmonary tuberculosis for many years. The diagnosis of bronchogenic carcinoma was based almost entirely on the radiological picture of the left lung, the pattern of progression of this lesion, and the absence of response of this fresh lesion to antituberculous therapy.

CASE 4.—L. B., a 45-year-old man, was admitted to the hospital on March 16, 1954. He had been a chain cigarette smoker for 30 years and had coughed for 10 years with expectoration of scant yellowish sputum. In January, 1954, a severe febrile coryza was followed by a persistent cough with substernal soreness and a weight loss of 6 lb. After a chest roentgenogram, he was directed to a tuberculosis hospital.

The physical examination revealed no abnormalities. Sputum and gastric cultures were persistently negative for tubercle bacilli. The tuberculin test was positive to 0.1 mg. O. T. The chest film of March 16, 1954, revealed streaky linear infiltrations extending from the right hilum to the right subapical region. This was believed to be due to old pulmonary tuberculosis. In the apical region of the left lung there was a dense homogenous ovoid opacity 4 cm. in diameter with a fuzzy circumference (Fig. 3). Bronchoscopy with biopsy and examination of the bronchial washings revealed no abnormalities. Normal lymph node tissue was found in the left scalene fat pad biopsy specimen.

On April 4, 1954, streptomycin and *p*-aminosalicylic acid was started, but this had no beneficial effect on the density of the left lung. On April 26,

1954, an exploratory thoracotomy revealed an inoperable squamous-cell carcinoma invading the thoracic wall. Postoperative recovery was uncomplicated; the patient has been receiving radioactive cobalt therapy.

Comment.—The diagnosis of old fibroid pulmonary tuberculosis was based on the long history of pulmonary symptoms and the roentgen appearance of the right lung. The diagnosis of bronchogenic carcinoma was derived almost wholly from the x-ray appearance of the left lung and the failure of this lesion to respond to antimicrobial therapy. Here, also, bronchoscopic, tissue, and cytological studies were of no assistance in the differential diagnosis because of the peripheral location of the tumor.

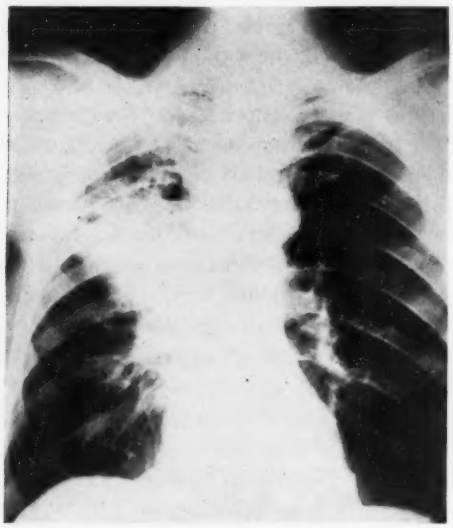


Fig. 4 (Case 5).—Active sputum-positive tuberculosis of right upper lobe. Large extremely opague wedge-shaped density at right hilum, with apex pointed toward axilla and linear streaks and spikes at its free borders, and enlargement of the hilum lymph nodes frequently seen with carcinoma of a stem bronchus.

CASE 5.—G. J., a 61-year-old man, who smoked 20 cigarettes daily throughout most of his life, was admitted to the hospital on June 6, 1954. He had coughed for 10 years, expectorating small amounts of white sputum. After July, 1953, the cough increased and he felt a dull pain on the right side of his chest anteriorly. He entered another hospital, where his sputum was found to contain tubercle bacilli and a diagnosis of pulmonary tuberculosis of the right upper lobe was made. Streptomycin and *p*-aminosalicylic acid converted his sputum to negative for tubercle bacilli, but there was progression of the disease nevertheless. In March, 1954, bronchoscopy at that hospital revealed a squamous-cell carcinoma.

On admission to Montefiore Hospital, the patient seemed to be in no distress and appeared to be well nourished. His fingers were clubbed. The trachea was fixed, and wheezes were heard throughout the right hemithorax. The chest film showed honeycombed cavitation throughout the right apex. At the right hilum there was a wedge-shaped density 8×8 cm., with its apex pointed toward the axilla and with linear streaks and broader spikes at its borders (Fig. 4). This appearance was rather typical of an infiltrating neoplasm of the larger bronchi with segmental atelectasis. The sputum remained persistently negative for tubercle bacilli.

Comment.—The diagnosis of pulmonary tuberculosis was based on a positive sputum and honeycombed cavitation of the right apex. The roentgen appearance was that of a carcinoma of the larger bronchi, and this was readily proved by bronchoscopy.

CASE 6.—E. S., a 65-year-old man, who was a heavy cigarette smoker with known pulmonary tuberculosis of 40 years' duration, was admitted to the hospital on April 28, 1954. He had been admitted to the hospital in 1914, 1935, and 1945 because of cough or hemoptysis, and each time the tuberculosis had been judged arrested and his sputum had been found negative for tubercle bacilli. In 1950 he was admitted because of a duodenal ulcer. After his discharge he was observed in the tuberculosis clinic until 1952, and he then disappeared from observation until his admission in April, 1954. In October, 1953, he began to note pain in the right posterior chest and his cough and expectoration increased. He lost 6 lb. and felt weak.

On admission, he still appeared well nourished. For the first time moderate clubbing of his fingers was noticed. Dullness and diminished breath sounds were elicited over the right upper lobe posteriorly. No palpable lymph nodes or lumps were felt. The admission chest x-ray now revealed an opacity in the entire right upper lobe with elevation of the horizontal fissure. Despite this lobar atelectasis, bronchoscopy revealed only slight narrowing of the right upper lobe bronchus, and no tumor cells were found in the bronchial exudate or the biopsy specimen of the bronchial mucosa. Normal fat and lymph glands were found in the scalene biopsy of April 30, 1954. A thoracotomy on June 3 revealed a large nonresectable anaplastic carcinoma involving the right upper lobe and the adjacent chest wall.

Comment.—The provisional diagnosis of bronchogenic carcinoma was based on the appearance of lobar atelectasis in the serial chest roentgenograms and was strengthened by the clinical features of persistent chest pain, increased cough and expectoration, and clubbing of the fingers. This diagnosis might have been made much earlier, before this extensive involvement of the lobar bronchus, had the patient not disappeared from roentgen observation for a period of two years.

COMMENT ON CASES

The six patients were all men between the ages of 45 and 69. Five of the six were admitted originally onto a tuberculosis ward over a 12-month period with a diagnosis of pulmonary tuberculosis, either active or activity to be determined. One was admitted directly to the nontuberculous pulmonary service, since activity of the tuberculous process had been ruled out by studies in the out-patient department.

Three patients were found to have active pulmonary tuberculosis with sputum positive for tubercle bacilli, and in two of these cases cavitation was demonstrable by x-ray. The other three cases were considered to have inactive pulmonary tuberculosis because of the stability of the lesions on serial x-rays and the failure to obtain positive sputum on culture.

In four of our patients, the diagnosis of a pulmonary neoplasm was suspected at the time of admission on the basis of the roentgenological appearance of the lesions. In Patients 2 and 4 a round homogenous density with fuzzy circumference aroused our suspicions. In Patient 5 the characteristic wedge-shaped lesion extending upward from the right hilum with linear projections at the periphery of the lesion made one strongly suspect a bronchogenic carcinoma. Case 6 had right upper lobe atelectasis with elevation of the horizontal fissure, which suggested a neoplasm of the appropriate bronchus.

In the remaining two patients the suspicion of malignant disease was raised when it was noted that there was extension and growth of the lesion on serial x-rays with concomitant regression of the tuberculosis elsewhere in the lungs on a regimen of adequate antituberculous chemotherapy and bed rest. This dichotomy between the effectiveness of therapy on two different lesions in the same organ is sufficient reason to suspect multiple pathologies. In Patients 1 and 3 it took six months in each case before the presence of carcinoma of the lung was considered. In retrospect, the homogeneity and opacity of the lesion on x-ray in Patient 1 might have suggested carcinoma prior to the further growth of the carcinoma.

There was one female patient, not included in this series, with active cavitary tuberculosis, in whom progression of infiltrations in the lung was demonstrated on x-ray, despite intensive chemotherapy which converted her sputum to negative. After 12 months of observation of such progression, histological examination of her abundant mucoid sputum established the diagnosis of alveolar-cell carcinoma, later confirmed on postmortem examination.

There was actually little in the histories of these patients that caused one to suspect carcinoma. All were heavy cigarette smokers and all had chronic coughs. Three of the six had at least one episode of hemoptysis. Only two patients had exertional dyspnea. Three had noted chest pain. Three patients were febrile. However, there were no symptoms that could not be explained by active pulmonary tuberculosis alone, with perhaps the exception of the persistent boring pains in the chest of Patient 6.

The most important physical sign that helped in differentiating between uncomplicated pulmonary tuberculosis and bronchogenic carcinoma was clubbing of the fingers. This was present in four of our six patients. Patient 5 had a localized wheeze, but, in this person, there was a neoplasm initially located in a major bronchus. The same patient had fixation of his trachea on vertical motion. Only in this case could the physical signs have suggested the diagnosis of pulmonary carcinoma.

The first bronchoscopy established the diagnosis of bronchogenic carcinoma in only one patient, Case 5. Only after the third attempt at needle biopsy were we able to confirm the diagnosis of primary lung cancer in Patient 1. Biopsy of nodes in the scalene fat pad in Patient 2 led to the diagnosis of inoperable carcinoma after more conservative confirmatory procedures had failed. In three patients, Cases 3, 4, and 6, exploratory thoracotomy revealed a bronchogenic carcinoma after bronchoscopy, bronchial washings, cytological studies of sputum, and scalene fat pad excisions had failed to confirm the diagnosis of these three suspected peripheral lung lesions.

Five of the six patients had peripheral lung carcinomas, while only one patient had a carcinoma of a stem bronchus. There were three squamous cell carcinomas, two adenocarcinomas, and one anaplastic carcinoma.

The pulmonary tuberculosis was not affected adversely by surgical or irradiation therapy of the coexistent bronchogenic carcinoma. One patient underwent a lobectomy for the carcinoma. The postoperative course was uneventful, and, although the carcinoma spread to the remainder of the left lung, the contralateral pulmonary tuberculosis has remained stable. One patient died of metastatic carcinoma. Four patients received intensive irradiation of the carcinoma, which could not be resected. There has been no evidence of a spread of the tuberculous infection in any of these cases.

GENERAL COMMENT

The diagnosis of pulmonary tuberculosis among these patients was not difficult, because the patients had either long known of their tuberculosis or the diagnosis had been adequately established in other hospitals prior to their present admission with bronchogenic carcinoma. Fried [9] and others have found that when both diseases are thought to coexist the pulmonary tuberculosis is usually known or strongly suspected prior to the consideration of neoplasia. In those patients with apparently arrested or inactive pulmonary tuberculosis, where the sputa and gastric washings were free of tubercle bacilli, this diagnosis was possible clinically because of the previous history of the disease and because there were serial x-rays over many years revealing the nonprogressive character of the tuberculosis. In the patients with active tuberculosis, cavitation was noted in the chest x-rays of two of our three cases and the sputa or gastric washings were found to contain tubercle bacilli in all three instances prior to therapy with antituberculous drugs. In these active cases of pulmonary tuberculosis, the advent of the bronchogenic carcinoma did not block the discovery of tubercle bacilli in the sputa; nor did the progression of the pulmonary carcinoma cause a reactivation of the pulmonary tuberculosis where the latter was previously inactive, although either of these eventualities was theoretically possible.

The diagnosis of coexistent bronchogenic carcinoma and pulmonary tuberculosis may be difficult because pulmonary tuberculosis and its complications can produce all of the clinical and roentgenological phenomena seen with carcinoma of the lung. There may be no reason to suspect that the patient with pulmonary tuberculosis is afflicted with any other disease. However, as the incidence of pulmonary tuberculosis increases among older age groups, the multiplicity of ailments found in any one patient likewise increases. Thus, Reiss and co-workers [10] found that 27% of their 70 patients with bronchogenic carcinoma had another chronic pulmonary disease and that 10% of these 70 patients had active pulmonary tuberculosis.

The diagnosis of coexistent pulmonary tuberculosis and bronchogenic carcinoma is not difficult clinically when the latter has invaded neighboring tissues or metastasized. A bronchogenic carcinoma with bloody pleural effusion; bone metastases; central nervous system metastases; invasion or stimulation of the cervical sympathetic chain, phrenic nerve, or recurrent nerve, or recurrent laryngeal nerve, or enlarged accessible lymph nodes is readily detected. Generally, where there is segmental or lobar emphy-

sema or atelectasis due to occlusion of the major bronchus, bronchoscopy or tomography rapidly yields proof of any coexisting carcinoma of the major bronchi. The tuberculous patient whose sputum becomes profuse and putrid may have a necrotizing carcinoma of the lung, and the sputum of such patients often contains malignant cells. Unfortunately, these findings can no longer be treated favorably by resection.

If the life of the patient is to be salvaged or prolonged, bronchogenic neoplasms must be discovered early, before spread to other tissues has occurred. Such neoplasms may produce no abnormal roentgen shadows or may produce small shadows which are missed or obscured by the normal contents of the thorax, making the diagnosis almost impossible, even in the absence of pulmonary tuberculosis. At times, it may not be possible to differentiate the early and small lesions of bronchogenic carcinoma from tuberculosis. However, the most useful and sometimes the only means of discovering small bronchogenic carcinomas is still the chest film, and for this purpose serial roentgenograms, views in various positions, tomography, and bronchography are of the greatest value.

There are certain subtle roentgenological differences which strongly favor the provisional diagnosis of bronchogenic carcinoma.

Infiltrates in the anterior segments of the upper lobe are often carcinomas, since similar tuberculosis lesions are more often located in the posterior segments.

Linear densities [11] resembling vascular shadows are at times roentgenological expressions of carcinoma. They differ from normal vascular shadows by being thicker, somewhat nodular, and failing to taper or branch at their periphery. Such lesions have been noted to grow into circumscribed larger nodules (Fig. 2*A*).

Faint veil-like and amorphous peripheral infiltrates may be either carcinoma [12] or tuberculosis (Fig. 2*B*). However, such carcinomatous lesions usually grow by concentric expansion, and the distal border frequently appears streaky or fuzzy owing to peripheral expansion of the neoplasm or focal atelectasis (Fig. 2*C*). Serial x-rays of these lesions show an increasing density and sharper demarcation of the tumor as the process progresses. Similar tuberculous foci are often accompanied by satellite tubercles, and streaking, when present, is usually found only at the medial border. Spread of tuberculosis is usually nodular or acinonodular owing to bronchogenic dissemination.

Dense round lesions which are carcinomatous usually have a fuzzy circumference and may, at times, become nodular or lobulated (Fig. 3). These are usually homogenous, rarely contain roentgen evidence of calcium, and often are accompanied by local obstructive emphysema or hilar gland enlargement. When there is a similar tuberculous lesion, it usually is less homogenous and may contain evidence of calicum or be associated with calcified peribronchial or hilar nodes. Localized obstructive emphysema practically never accompanies such tuberculomata.

Unilateral enlargement of the hilum is both the commonest and perhaps the most frequently overlooked roentgenological evidence of bronchial carcinoma.[11] When no peripheral lesion is visualized, this usually indicates a neoplasm involving the large bronchus. In serial films the carcinoma or the affected hilar glands may be observed to grow. In Americans past 40 years of age, tuberculous hilar glands have rarely been noted to enlarge on subsequent roentgen examinations.

Tumors of the large bronchi, when too small to be seen in single chest films, may at times be appreciated by tomography. Larger tumors of major bronchi produce infiltrating densities at the hilum with fine or broader strand-like peripheral projections extending fan-like from the central density. The x-ray pictures of these tumors are often dominated by the appearance of partial or complete stenosis of the bronchus, manifested by segmental, lobar, or whole lung emphysema or atelectasis, respectively. The shinkage of the involved lung first results in an elevation of the diaphragm or an appropriate shift of the interlobar fissures and later in an increased

density of the involved portion of the lung. Complete atelectasis of a lobe or lung may be accompanied by secondary infection, suppuration, and abscess formation. Even in the presence of inflammation or atelectasis, in the same lobe or segment, the hard dense central core of tumor can often be distinguished from the collapsed or inflamed lung by laminograms or Bucky films. Pulmonary tuberculosis may occur about the hilum but rarely produces the strand-like projections noted with bronchogenic carcinoma. Stenosis of the larger bronchi is sometimes caused by endobronchial tuberculosis or is a result of a caseous hilar node in childhood compressing or eroding into the bronchus. The latter occurs most frequently in the right middle lobe. The resulting atelectasis produces a density which is homogenous and cannot be separated into component parts by any roentgenological technique. When the atelectasis is the result of a tuberculous lymphadenopathy, the involved hilum glands are usually calcified.

The cavities which form as a result of suppuration or anemic necrosis of a bronchogenic carcinoma are usually distinctive. Because of its thick wall, the carcinomatous cavity is poorly penetrated by the roentgen ray and is poorly visualized. The cavity is eccentrically placed in the opacity caused by the tumor. The wall of the cavity is often irregular or scalloped, with projections of tumor tissue into the cavity. Tuberculous cavities usually have thinner and smoother walls, and the contents of the cavities are more easily visualized and are homogenous. The size of the tuberculous cavity may be noted to shrink or balloon with changes in intrabronchial or intrapleural pressures, and under appropriate therapy the cavity may become smaller and disappear. The carcinomatous cavity does not balloon, shrink, or disappear under treatment. However, the abscessed cavity in a lobe distal to an obstructing tumor can rarely change in size during therapy for tuberculosis.

Tumors occupying the superior sulcus of the chest are distinguished roentgenologically by their frequent erosion and invasion of the first and second ribs. Apical tuberculosis does not produce such changes in the bone. The Pancoast tumors stimulate or interrupt the upper cervical sympathetic chain and the brachial plexus. The resulting changes in the pupil of the eye, the levator palpebrae oculi, and the attendant vasomotor phenomena together with pain along the brachial plexus nerves are never seen in tuberculosis of the same region.

Ancillary roentgenographic procedures are extremely helpful in differentiating bronchogenic carcinoma from pulmonary tuberculosis. Films taken in the oblique and lateral positions may demonstrate tumors not visualized in the posterior-anterior projections. Films taken in expiration best reveal obstructive emphysema. Tomograms not only demonstrate the extent of the neoplasm, disassociating it from any accompanying infection or atelectasis, but frequently reveal changes within the bronchus indicative of neoplasm. The bronchus infiltrated by or containing a carcinoma appears irregular, and the tumor at times may be seen to project into it. The peribronchial invasion produces a cuff-like shadow [13] surrounding the proximal end of the involved bronchus, whereas tomograms of the tuberculous bronchus show only a smooth narrowing or occlusion. Tuberculosis sometimes involves several scattered bronchi, whereas carcinoma involves a continuous section of the bronchial tree. Bronchography can likewise demonstrate the caliber and content of the bronchial tree and may thus aid in the diagnosis of bronchogenic carcinoma; however, if iodized oil is used it may remain for long periods, obscuring later films and delaying resection where this seems feasible. Bronchoscopy is a far more useful and preferable procedure, since it does not leave residual oil in the lung and permits the simultaneous removal of tissue or exudate for examination. Angiography may reveal malignant invasion and obstruction of vascular structures. However, this procedure is rarely necessary in view of the difficulties and risk involved.

When bronchogenic carcinoma is suspected in patients with pulmonary tuberculosis, valuable auxiliary information may be obtained by bronchoscopy, biopsy, aspiration biopsy, removal of the scalene fat pads, and examination of the cells in the bronchial secretion. When a bronchogenic carcinoma is present, positive confirmation by these methods is most apt to be found when the tumor arises in the larger and more proximal bronchi. When the tumor is peripheral or apical and has not metastasized, positive confirmation is frequently not obtained by these procedures. Such confirmation of the carcinoma, present in these six patients, was obtained in only three instances, and in two of these, only after delays of six to nine months.

Patients with pulmonary tuberculosis whose roentgenograms suggest the advent of a bronchogenic carcinoma should immediately be placed on combined and adequate therapy with streptomycin, isoniazid, and *p*-aminosalicylic acid for three to four weeks to force a regression of the suspected lesion if this proves tuberculous. If regression occurs, this treatment should be continued. During this short period all confirmatory studies listed should be finished, and the patient's ability to withstand chest exploration and possible pneumonectomy should be improved. Should these studies demonstrate a carcinoma limited to the lung and not involving the scalene fat pads or the carina, exploration of the lesion with the hope of resecting the involved lung should be attempted therewith. When the suspicion of an operable bronchogenic carcinoma persists, even if it is based entirely on roentgenological grounds with negative confirmatory studies, the suspected lesion should be explored for diagnosis and possible resection without further delay for repetitive ancillary diagnostic procedures.

SUMMARY AND CONCLUSIONS

There appears to be an increased frequency of coexisting bronchogenic carcinoma and pulmonary tuberculosis. Over a 12-month period at Montefiore Hospital, there were six patients in whom these two diseases were found. These cases are described in detail. In all of these the roentgenological appearance of the lesion was the primary factor in the diagnosis. When the confirmatory diagnostic studies such as bronchoscopy, cytological examination of the sputum and bronchial washings, biopsy of bronchial mucosa, and excision of the scalene fat pads failed to provide a definitive diagnosis, exploratory thoracotomy was resorted to on the basis of roentgenological findings alone. The various x-ray manifestations of bronchogenic carcinoma are described, from the minute linear density through the veil-like peripheral infiltrate and the round-coin lesion to the more obvious large central tumors with segmental or lobar emphysema or atelectasis. In any patient who shows roentgenological regression of tuberculous densities on rest and adequate chemotherapy and simultaneous growth or failure of another noncalcific lesion to improve, one may strongly suspect the coexistence of carcinoma of the lung and pulmonary tuberculosis.

At present, the only opportunity for making an early diagnosis of lung cancer before symptoms and signs develop is based almost wholly on chance x-ray examination of the chest.[14] Patients with pulmonary tuberculosis present a unique opportunity for early discovery of bronchogenic carcinoma, since they undergo frequent serial roentgenological examinations of their chests. With the increased frequency of lung cancers and with the shifting incidence of pulmonary tuberculosis into the older age groups, it is important for physicians treating pulmonary tuberculosis to be conscious of the increasing incidence of bronchogenic carcinoma in these patients.

REFERENCES

1. Hamilton, G. E., and Wexler, N. H.: Carcinoma and Tuberculosis of the Lung, Am. Rev. Tuberc. **42**:234 (Sept.) 1940.

2. Cooper, F. G.: The Association of Tuberculosis and Carcinoma, Am. Rev. Tuberc. **25**:108 (June) 1952.

3. Drymalski, G. W., and Sweany, H. G.: The Significance of Pulmonary Tuberculosis when Associated with Bronchogenic Carcinoma, Am. Rev. Tuberc. **58**:203 (Aug.) 1948.

4. Gerstl, B.; Warring, F. C., Jr., and Hewlett, K. S., Jr.: Cancer and Pulmonary Tuberculosis: Diagnostic Problems in Patients with Cancer of the Lung in the Presence of Pulmonary Tuberculosis, Am. Rev. Tuberc. **54**:470 (Dec.) 1946.

5. de la Fuente, M. L., and Palacios, R. H.: Undifferentiated Cell Carcinoma of Lung and Chronic Pulmonary Tuberculosis, Quart. Bull., Sea View Hosp. **7**:314, 1942.

6. Goldberg, J.; Figueros, E. R., and Barshay, B.: Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis, Dis. Chest **21**:184 (Feb.) 1952.

7. Woodruff, C. E., and Nahas, H. C.: Pulmonary Tuberculosis, Bronchiectasis and Calcification as Related to Bronchigenic Carcinoma, Am. Rev. Tuberc. **64**:620 (Dec.) 1951.

8. Robbins, E., and Silverman, G.: Coexistent Bronchogenic Carcinoma and Active Pulmonary Tuberculosis, Cancer **2**:65, 1949.

9. Fried, B. M.: Bronchogenic Cancer Combined with Tuberculosis of the Lung, Am. J. Cancer **22**:247 (Feb.) 1935.

10. Reiss, J.; Baum, G. L., and Kovnat, M.: The Early Recognition and Treatment of Bronchogenic Carcinoma, Dis. Chest **22**:529 (Nov.) 1952.

11. Rigler, L.; O'Loughlin, B., and Tucker, R. C.: The Duration of Carcinoma of the Lung, Dis. Chest **23**:150 (Jan.) 1953.

12. Siltzbach, L.: Carcinoma Simulating Tuberculosis, Am. Rev. Tuberc. **55**:170 (Feb.) 1947.

13. Rabin, C. B.: X-Ray Diagnosis of Chest Diseases, Baltimore, Williams & Wilkins Company, 1952.

14. Schinz, H. R.; Baensch, W. E.; Friedl, E., and Uehlinger, E.: Roentgen Diagnosis, Vol. 3, Thorax, New York, Grune & Stratton, Inc., 1953.

The Use of Chlorpromazine in the Management of Patients with Head Injury

JAMES G. SHEA, M.D.
RALPH W. ALMAN, M.D.
and
JOSEPH F. FAZEKAS, M.D., Washington, D. C.

The antiemetic and tranquilizing properties of chlorpromazine have proved to be of great value in the management of acute and postalcoholic states. The high incidence of head injuries in the alcoholic population makes it important to determine whether the use of chlorpromazine, a central nervous system depressant, might be contraindicated in the presence of head injury or whether it may be a more desirable sedative than those currently available. This report concerns its use in the management of patients with head injuries.

MATERIAL

The subjects of the present study were patients admitted to the District of Columbia General Hospital because of head injuries with or without acute alcoholism. All subjects exhibited a disturbed mental condition. After clinical evaluation, 50 to 100 mg. of chlorpromazine was administered, in most instances orally or intramuscularly; in several cases its administration was necessary for the successful completion of diagnostic studies and clinical observations. The dose was repeated as required until control of the excitatory state was achieved.

The Table summarizes pertinent data obtained in the subjects studied. The following abbreviated case histories present a more detailed description of representative observations.

Submitted for publication May 26, 1955.

From the District of Columbia General Hospital.

The chlorpromazine (Thorazine) used in this study was supplied by Smith, Kline & French Laboratories, Philadelphia.

REPORT OF CASES

CASE 1.—A 49-year-old man with a history of chronic alcoholism was admitted to the hospital because of an episode of unconsciousness and stupor resulting from trauma to the left temporal region. For 12 days prior to admission he had been drinking heavily.

The patient was disoriented, hyperactive, and belligerent and resisted attempts at examination. He was given 50 mg. of chlorpromazine intravenously, and within 20 minutes physical examination as well as lumbar puncture were performed without resistance. The blood pressure was 140/100; respirations, 20 per minute; pulse rate, 100 per minute, and temperature, 100 F. Positive findings were swelling over the left eye and temporal region, palpable liver, palmer erythema, generalized tremulousness, and hyperactive reflexes. There were no abnormal spinal fluid findings, and skull x-rays were normal.

The patient received 50 mg. of chlorpromazine orally every 6 hours for 48 hours and made an uneventful recovery. The administration of chlorpromazine in this case permitted necessary diagnostic studies and made the patient more easily manageable.

CASE 2.—A 55-year-old known epileptic was admitted to the hospital because of a generalized convulsive seizure resulting in a laceration over the right occipitoparietal region. He admitted having had a high alcohol intake for one week prior to admission. Because of the patient's extreme agitation, examination and emergency treatment were not possible. He was given 50 mg. of chlorpromazine intramuscularly, and within 45 minutes the head laceration could be sutured. His blood pressure was 145/90; pulse rate, 90 per minute; respirations, 24 per minute, and temperature, 99 F. Physical examination was essentially normal, as were the spinal fluid findings. During the 48 hours the patient was under observation, he received 50 mg. of chlorpromazine orally every 6 hours. All procedures and examinations were carried out with his full cooperation. There were no convulsive episodes, and the patient was dicharged on a regimen of diphenylhydantoin (Dilantin) and phenobarbital.

Clinical Observations Before and After Chlorpromazine

Diagnosis	Av. Blood Pressure *		Spinal Fluid	Skull X-Ray	Degree of Agitation *		Chlorpromazine	
	C	E			C	E	Total Dosage, Mg.	Duration of Therapy, Days
Concussion; delirium tremens	140/100	140/90	Neg.	Neg.	4	1	500	5
Concussion; epilepsy; occipital laceration; acute alcoholism	145/95	130/80	Neg.	None	4	1	350	2
Middle fossa fracture; subdural hematoma; acute alcoholism	130/80	120/70	Grossly bloody and increased pressure	Fracture	3	1	1,800	9
Concussion; contusion; acute alcoholism	160/100	140/90	Neg.	None	4	2	500	3
Concussion; nasal fracture; acute alcoholism	150/100	130/85	Neg.	Nasal fracture	3	1	100	1½
Cerebral contusion; laceration, left ear	150/100	140/100	180 RBC's	Neg.	3	0	450	2
Concussion	160/90	130/80	Neg.	None	3	0	150	1½
Concussion; laceration, forehead	140/90	130/80	Neg.	None	2	0	200	1
Concussion; laceration, eyebrow	140/110	140/100	Neg.	Neg.	3	0	750	3
Concussion; laceration, scalp	150/110	140/90	Neg.	None	4	0	500	3
Concussion; laceration, scalp	140/95	130/80	Neg.	Neg.	3	0	400	3
Concussion; lacerations, face and scalp	160/100	140/80	Neg.	None	4	1	600	4

* C, before chlorpromazine; E, during chlorpromazine. Degree of agitation is indicated by numerals from 0 to 4, as follows: 0, somnolence; 1, rational; 2 mild agitation; 3, moderate agitation, and 4, severe agitation.

This case demonstrates that postconvulsive excitement may be controlled by the administration of chlorpromazine and again indicates its usefulness for diagnostic and therapeutic measures.

CASE 3.—A 45-year-old man was admitted to the hospital because of unconsciousness resulting from a fall four hours prior to admission. The patient was conscious but lethargic on arrival and complained of severe headache. He was bleeding from the right ear. He was uncooperative but oriented. Blood pressure was 135/90; pulse rate, 70 per minute; respirations, 20 per minute, and temperature, 98.6 F. The only abnormal neurological finding was anisocoria. Skull x-ray revealed a right middle fossa fracture, and lumbar puncture disclosed an initial pressure of 210 mm. H_2O, a final pressure of 155 mm. H_2O, and grossly bloody fluid in all tubes. The patient was given 50 mg. of chlorpromazine orally every six hours for nine days. His blood pressure fell moderately (to 100/60) following chlorpromazine administration, and he slept intermittently but was always easily aroused for neurological evaluation. On the ninth hospital day he complained of vertigo and developed a right-sided peripheral seventh nerve paralysis. A repeat lumbar puncture revealed initial pressure to be 260 mm. H_2O and final pressure to be 160 mm. H_2O. The fluid was xanthochromic and contained 100 RBC per cubic millimeter. On the tenth hospital day weakness and tremor of the left hand and arm and a visual defect in the left eye were noted. Exploration revealed a subdural hematoma in the left parietal region. In this instance the patient complained of such severe headache that it was necessary to give salicylates and codeine concomitantly with chlorpromazine. The subsequent clinical course was not remarkable, and the patient was discharged without neurological residua. This case illustrates the effectiveness of chlorpromazine in the more serious type of head injury and its apparent safety with respect to aggravation of depression or masking of important neurological signs.

COMMENT

Sedatives and analgesics are highly desirable and sometimes necessary adjuvants in the management of patients with head injuries. Unless such agents are employed to relieve pain or reduce excitement, some of these often irrational patients may become extremely difficult to manage and possibly even suffer additional trauma. An ideal sedative for such cases should allay excitement without causing stupor. It should not mask signs of existing or progressing neurological damage; it should materially relieve the patient of pain or reduce the amount of anal-

respiration or otherwise aggravate the effects of head injury, nor should it have undesirable properties or side-effects less directly pertaining to the central nervous system. It is recognized that most sedatives and hypnotics currently available when given in effective concentrations usually fall short of the above-described ideal in one or another respect. In contrast, we have been favorably impressed upon examining chlorpromazine according to these criteria.

In all cases studied, this drug produced satisfactory tranquilization, even in those instances of excitement due to head injury without acute alcoholism. In several subjects, lumbar puncture and x-rays of the skull were readily performed after the administration of chlorpromazine, although active resistance had made these procedures impossible beforehand. There was little difficulty in retaining intravenous infusion needles, nasal oxygen tubes, or urethral catheters, and nursing procedures were greatly facilitated. Since, as has been previously indicated,[1] chlorpromazine appears to have a selective action upon specific areas of the central nervous system rather than producing a descending depression, the sleep which it induces is not due to direct suppression of cortical activity. Most patients can therefore be aroused to essentially the same degree of alertness present before adminstration of the drug. Where evidence of increased cortical depression is noted upon such attempts, causes other than the effects of chlorpromazine should be searched for and adminstration of the drug should be discontinued. We are aware of only two instances in which a paradoxical response appeared to be induced by the administration of chlorpromazine. A normal subject (without head injury) became agitated and hyperactive after receiving only 12.5 mg. of the drug. The patient again became calm after approximately three hours. Unfortunately, it could not be determined whether the reaction was one of unusual sensitivity to the drug or an emotional reaction not related to its pharmacological effects. Another subject with acute alcoholic tremulousness was given 50 mg. of chlorpromazine every six hours, and it was noted that after each administration he became more excited and disoriented and had an elevation in pressure. The drug was discontinued for 12 hours, and he was then given 25 mg. of chlorpromazine. Within 35 minutes, the patient's blood pressure rose from 140/90 to 160/110, his pulse increased from 90 to 130, and he again became excited and hyperactive.*

In a separate study, designed to investigate the possible masking or misleading effects of chlorpromazine upon certain reflexes, four ambulatory convalescent tuberculous subjects were each given two oral doses of 50 mg. of chlorpromazine one hour apart. Immediately before the first dose and one hour after each dose, careful evaluation was made of gag reflex, cough reflex (as determined by reaction to nebulized 10% citric acid), corneal reflex, tendon reflexes, and muscle proprioception. In order to minimize somnolence, which might have made this evaluation difficult, all of these subjects remained together and were permitted unrestricted conversation and activity during the period of observation. Of the various reflexes and functions tested, none showed either impairment or exaggeration, even after the second dose of chlorpromazine. Thus, it appears that this drug does not interfere with those reflexes the demonstration of which is the conventional guide for estimating the patient's neurological status. Moreover, it appears not to depress appreciably the gag or cough reflexes. The latter two are particularly important, not so much for clinical observation and evaluation of the patient but rather as necessary protective reflexes which may often be suppressed by other sedative agents or cerebral complications secondary to head injury.

If analgesics are required for any reason or if convulsions necessitate the administration of a cortical depressant, satisfactory results usually attend dosage guided by the

* Dr. Alvin E. Parrish called one of these patients to our attention.

knowledge that the action of many of these drugs is significantly potentiated by chlorpromazine. At the present time the opium alkaloids, synthetic narcotics, and aliphatic hypnotics have been demonstrated to participate in this potentiating action.[2] Therefore, only about one-half of the usual doses are required when chlorpromazine is given concomitantly. It may be mentioned that in animal experiments chlorpromazine itself raises the convulsive threshold to certain central stimulating drugs.[2] In addition to potentiating the narcotic analgesics, chlorpromazine, by causing dissociation of subcortical from cortical centers, modifies the reaction to painful stimuli and in this manner may itself relieve the patient of pain.[2] In the present group of subjects, the concomitant use of a mild analgesic was required in only one instance.

There has been no evidence to indicate that chlorpromazine in therapeutic concentrations has any adverse effect upon the respiratory mechanism. In none of the cases of this series nor in any of more than 500 other subjects receiving chlorpromazine have we observed any evidence of respiratory depression. The drug did not appear to aggravate cerebral edema or intracranial bleeding. The single fairly common undesirable side-action of chlorpromazine was its tendency to produce hypotension and tachycardia. With rapidly increasing intracranial pressure due to acute cerebral edema or intracranial bleeding, an increase in blood pressure is a compensatory mechanism for maintaining an adequate cerebral circulation. Hypotension resulting from the administration of chlorpromazine might theoretically in such cases be harmful. Fortunately, in most instances, the reduction in blood pressure produced by chlorpromazine is of slight-to-moderate degree and unlikely to have any adverse effect upon cerebral circulation. Moreover, the occasional patient who demonstrates a marked hypotensive response usually does so with the first dose of chlorpromazine, presumably at a time sufficiently early so that an expanding lesion would not yet have placed him in maximum danger. In this series, vascular collapse attributable to chlorpromazine was not observed.

In our experience, the optimum initial dose of chlorpromazine ranges between 25 and 50 mg., depending upon the degree of hyperactivity of the patient. Occasionally with extreme excitement a dose of 100 mg. may be indicated. It is usually necessary in the cases under consideration to administer the drug by deep intramuscular injection, following which appreciable effects are demonstrable in about 30 minutes. If there appears to have been no significant effect, the dose may be repeated within an hour. The indications for subsequent administration depend chiefly upon clinical observation. Usually a single dose will be effective for approximately four to six hours. The amount administered should depend upon the quantity previously determined necessary for sedation and the clinical state of the subject.

SUMMARY

Chlorpromazine was administered to 11 disturbed subjects with various types of head injuries, some associated with acute alcoholism. The drug permitted diagnostic and therapeutic measures to be carried out and maintained the patients in a tranquilized state from which they could be easily aroused for neurological evaluation. The advantages as well as the disadvantages of the drug for the treatment of such cases are discussed.

REFERENCES

1. Laborit, H.; Huguenard, P., and Allaume, R.: Un Nouveau Stabilisateur végétatif (le 4560 RP), Presse méd. **60**:206-208 (Feb. 13) 1952.

2. Courvoisier, S.; Fournel, J.; Ducrot, R.; Kolsky, M., and Koetschet, P.: Propriétés pharmacodynamiques du chlorhydrate de chloro-3(diméthylamino-3′-propyl)-10 phénothiazine (4560 R. P.): Etude expérimentale d'un nouveau corps utilisé dans l'anesthésie potentialisée et dans l'hibernation artificielle, Arch. internat. pharmacodyn. **92**:305-361, 1953.

Marked Hypernatremia and Hyperchloremia with Damage to the Central Nervous System

SAMUEL NATELSON, Ph.D.
and
M. O. ALEXANDER, M.D., Rockford, Ill.

The recent paper of Schoolman and coworkers [1] on the syndrome of hypernatremia and hyperchloremia * draws the categorical conclusion, "the treatment of hypernatremia is the intravenous or oral administration of non-saline fluids. Such treatment is usually successful except in cases of central nervous system injury severe enough to produce death."

We take issue with this conclusion, since it suggests that this treatment should be followed for all cases in which the high-salt syndrome is observed. It is our contention that if this treatment is pursued, in certain cases, to its logical conclusion it will result in salt depletion and its attendant sequelae, before the sodium and chloride levels are brought to what is considered "normal" levels for the healthy person. As typical examples, two cases are cited.

CASE 1.†—A 3-month-old infant was admitted because of lack of gain in weight and dehydration. Birth weight was 7 lb., 12 oz.; weight on admission was 7 lb., 10 oz. The infant responded clinically to intravenous fluid therapy with solutions of ⅙ M lactate and isotonic saline 2:1 diluted 1:5 with 5% dextrose in water, but the salt levels became high (Table 1). After the second day the infant was given a diluted formula of homogenized cow's milk. Urine specific gravity was 1.002 to 1.005 and remained essentially the same after the water-deprivation test. With normal hydration urine output was large, and a diagnosis of diabetes insipidus was made. Pneumoencephalography suggested to the consultant a diagnosis of "diffuse cortical atrophy of the brain." At nineteen months of age the child weighed 15 lb., 12 oz. and still showed symptoms of diabetes insipidus. The high-salt syndrome was still evident (Na, 165 mEq/L.; Cl, 120 mEq/L.; K, 4.5 mEq/L.).

CASE 2.‡—A 67-year-old farmer had fallen 20 ft., from a silo. He had sustained head bruises but no fractures. From the time of admission the swallowing reflex was impaired, and spoon and tube feeding was resorted to. He became comatose and developed the high-salt syndrome 14 days after admission. When the high sodium and chloride levels were observed on the 14th day (Table 2), 4000 ml. of invert sugar in water with 80 mEq. of potassium, vitamins, and 2000 ml. of 5% protein hydrolysate were administered over a 48-hour period. This resulted in a diuresis and dehydration with elevation of the urea level. Sodium and chloride levels remained the same. From the 16th hospital day, fluids administered included 10 to 15 gm. of NaCl daily. In spite of the added salt, a continuous lowering of the sodium and chloride levels was observed after the 20th day. Potassium levels were slow in

Submitted for publication March, 30, 1955.
From the Laboratories of the Rockford Memorial Hospital.

* These authors refer to this syndrome as hypernatremia. Both chloride and sodium levels are elevated in this condition.

† Case of Charles H. Kurtz, M.D.

‡ Case of Maurice P. Rogers, M.D.

TABLE 1.—*Chronic Hypernatremia and Hyperchloremia in an Infant with Diffuse Cortical Atrophy of the Brain Showing Symptoms of Diabetes Insipidus: Blood and Serum Levels of Pertinent Constituents*

Hospital Day	Na, mEq./L.	Cl, mEq./L.	K, mEq./L.	Protein, Gm./100 Cc.	Hematocrit Value, %	Blood pH	Urea, Mg./100 Ml.
1	145	115	4.6	6.9	37	7.26	24.0
2	165	135	4.0	6.4	35	7.41	16.8
6	158	128	4.6	5.0	34	7.39	12.2
10	158	126	4.1	5.8	35	7.37	13.1

TABLE 2.—*Blood and Plasma Levels of Pertinent Constituents in a Sixty-Seven-Year-Old Man Following Head Injury, Illustrating Hypernatremia and Hyperchloremia Which Did Not Respond to Nonsaline Fluids but Spontaneously Returned to Normal on Fluids Containing the Normal Daily Salt Requirement*

Hospital Day	Urea N, Mg./100 Ml.	Protein, Gm./100 Cc.	Na, mEq./L.	K, mEq./L.	Cl, mEq./L.	Hematocrit Value, %
14	24.0	5.9	168	4.5	125	46
16	37.4	6.3	173	3.6	130	52
17	27.2	5.6	173	3.3	140	43
19	19.5	...	171	3.3	133	43
20	35.6	5.1	168	3.2	128	40
21	....	4.1	159	3.3	118	..
22	34.6	5.3	165	3.6	123	..
23	25.1	5.0	165	3.3	115	..
26	17.8	5.3	145	2.7	109	..
27	14.6	5.0	143	2.8	101	35
28	12.0	4.3	146	2.8	100	..
33	18.2	5.5	143	3.3	95	41
43	9.8	6.3	140	4.3	105	40

returning to normal, although intravenous fluids contained the amount lost in the urine plus an amount calculated to correct extracellular deficit. This may have been due to large intracellular deficit sustained before intravenous fluids were initiated. Blood and plasma were administered from time to time to maintain erythrocyte count and plasma protein levels, in addition to daily administration of 50 to 75 gm. of protein hydrolysate. Urine specific gravity ranged from 1.016 to 1.025. The patient regained consciousness on the 49th day. In all, the patient was on total or partial intravenous fluids for 54 days. He was dismissed on the 67th day in improved condition but in a wheelchair. Two years later, at 69 years, he was engaged in vigorous farm work in good health.

COMMENT

The two cases cited exhibited the hypernatremia and hyperchloremia associated with symptoms of central nervous system damage. The levels of both sodium and chloride remained high in the absence of symptoms of dehydration. The underlying cause for the pathology resulting in the high-salt syndrome was reversible in Case 2 but not in Case 1.

Case 1 is similar to the case described by Engstrom and Liebman,[2] in which the high-salt syndrome was associated with Cushing's syndrome and diabetes insipidus. Except for the first 24 hours, when the infant was treated for acidosis and dehydration, responding promptly, this infant appeared in fair general health. As indicated, at 19 months of age the salt levels were still high on a normal diet.

Case 2 showed a tendency to high plasma sodium and chloride levels for a 10-day period regardless of whether the fluids administered did or did not contain salt. Withholding of salt merely resulted in a reduction of plasma volume to a critical point, as indicated by the clinical condition and the rise in hematocrit and protein levels.

That the high-salt syndrome may exist, chronically, with brain damage in the absence of symptoms of dehydration or kidney disease has been adequately demonstrated in the reports of Allot,[3] Cooper and co-workers,§ Engstrom and Liebman.[2] Lack of appreciation of this phenomenon has resulted in misinterpretation, in some reports, of the significance of high plasma sodium and chloride levels which are not lowered by prolonged treatment with nonsaline fluids. Examples of such reports are those of Schoolman and coworkers,[1] Montgomery,[6] and some of the cases of Rapoport.[7]

It is noteworthy that Schoolman [1] points out, in the condition he calls "primary desiccation syndrome," that "in all instances the diarrhea was mild." For example, in Case 3 of Schoolman's report (page 15) the author

§ References 4 and 5.

reports on a dehydrated infant admitted with a sodium and chloride level of 166 mEq/L. and 131 mEq/L., respectively. In this 9-month-old infant high plasma sodium and chloride levels persisted (sodium 151 mEq. and chloride 124 mEq/L.) after 48 hours on nonsaline fluids (2000 ml.). Further, a mild convulsion was noted, and the infant was treated with 30 mg. of phenobarbital. Subsequently this infant was given fluids by mouth which contained the daily salt requirement.‖ The electrolyte levels then gradually returned to normal.

Case 1 of this report and the case of Engstrom and Liebman [2] indicate that the high-salt syndrome may persist indefinitely in certain persons. This suggests a center or centers which maintain the sodium chloride levels in a steady state.[8] In pathological conditions in which these levels are high, withdrawal of salt from the diet will result in a decreased extracellular fluid volume, just as it does in the person with "normal" salt levels.[9] If withheld indefinitely, a point is reached where further administration of nonsaline fluids will serve to dilute the extracellular fluid and lower these values to what appears "normal" values for the healthy person but is low for these patients. This results in the same symptoms observed in healthy persons with excessive salt loss.

The condition of high-salt syndrome has been frequently observed in this hospital in association with cerebrovascular accident, encephalitis, following severe dehydration, and following a period of anoxia in the premature. Others have observed this condition in patients in whom brain damage was secondary to some other disease.¶ The condition of hypernatremia and hyperchloremia is often reversible in these cases. However, the period of time required for repair of those centers responsible for this syndrome is indeterminate. Thus, continuing with nonsaline solutions indefinitely in the expectation of bringing the plasma sodium and chloride levels to normal, may result in salt depletion to a critical point.

In the light of the above discussion, the logical conclusion seems to be that when markedly elevated plasma sodium and chloride levels are noted, and when they persist after the patient has been treated for a prolonged period of time (24 to 48 hours) with apparently adequate volumes of nonsaline fluids, then one must assume that these high levels are evidence of a pathological condition of the center or centers controlling the sodium and chloride levels and fluids subsequently administered should contain the amount of salt required to replace losses through the urine, and sweat, stool, and drainage fluids, if any.

‖ Dubin, A.: Personal communication to the authors.

¶ References 10-13.

SUMMARY

Two examples are given to illustrate the phenomenon that with brain damage high plasma sodium and chloride levels may persist in patients with adequate hydration. It is pointed out that complete withholding of salt from these patients for extended periods of time will result in symptoms usually associated with excessive salt loss, before the plasma sodium and chloride levels are brought to values which are considered "normal" for healthy persons.

REFERENCES

1. Schoolman, A. M.; Dubin, A., and Hoffman, W. S.: Clinical Syndromes Associated with Hypernatremia, A. M. A. Arch. Int. Med. **95**:15, 1955.

2. Engstrom, W. W., and Liebman, A.: Chronic Hyperosmolarity of the Body Fluids with a Cerebral Lesion Causing Diabetes Insipidus and Anterior Pituitary Insufficiency, Am. J. Med. **15**:180, 1953.

3. Allot, E. N.: Sodium and Chloride Retention Without Renal Disease, Lancet **1**:1035, 1939.

4. MacCarthy, C. S., and Cooper, I. S.: Neurologic and Metabolic Effects of Bilateral Ligation of the Anterior Cerebral Arteries in Man, Proc. Staff Meet., Mayo Clin. **26**:185, 1951.

5. Cooper, I. S., and MacCarthy, C. S.: Unusual Electrolyte Abnormalities Associated with Cerebral Lesions, Proc. Staff Meet., Mayo Clin. **26**:354, 1951.

6. Montgomery, R.: Clinical Conference at the Los Angeles Childrens Hospital: Case 2: Hyperelectrolytemia and Hyperosmolarity in an Infant, J. Pediat. **42**:742, 1953.

7. Rapoport, S.: Hyperosmolarity and Hyperelectrolytemia in Pathological Conditions of Childhood, Am. J. Dis. Child. **74**:682, 1947.

8. Natelson, S.: Abnormality in Blood Electrolyte Patterns with Injury to the Brain, Fed. Proc. **13**:268, 1954.

9. Muntwyler, E., and Mautz, F. R.: Electrolyte and Water Equilibria in the Body, in Medical Physics, edited by O. Glasser, Chicago, Year Book Publishers, Inc., 1944, p. 375.

10. Leutscher, J. A., Jr., and Blackman, S. S., Jr.: Severe Injury to Kidneys and Brain Following Sulfathiazole Administration: High Serum Sodium and Chloride Levels and Persistent Cerebral Damage, Ann. Int. Med. **18**:741, 1943.

11. Goodale, W. T., and Kinney, T. D.: Sulfadiazine Nephrosis with Hyperchloremia and Encephalopathy, Ann. Int. Med. **31**:1118, 1949.

12. Borst, J. G.: Cause of Hyperchloremia and Hyperazotemia in Patients with Recurrent Massive Hemorrhage from Peptic Ulcers, Acta med. scandinav. **97**:68, 1938.

13. Sweet, W. H.; Cotzias, G. C.; Seed, J., and Yakovlev, P. I.: Gastrointestinal Hemorrhage, Hyperglycemia, Azotemia, Hyperchloremia and Hypernatremia Following Lesions of Frontal Lobe in Man, A. Res. Nerv. & Ment. Dis., Proc. **27**: 795, 1948.

The Hazard of Unrecognized Catheterization of the Coronary Sinus

JOHN L. READ, M.D.
EDWARD G. BOND, M.D.
and
RENO R. PORTER, M.D., F.A.C.P., Richmond, Va.

Catheterization of the heart, originally performed by Forssmann,[1] its physiologic application perfected by Klein,[2] and utilized as an important diagnostic method by Cournand and Ranges,[3] Bing,[4] and Dexter,[5] has made possible a new era in the diagnosis and surgical alleviation of a variety of cardiovascular lesions, both congenital and acquired. The usual complications of this procedure consist of auricular and ventricular extrasystoles or more sustained arrhythmias, and their frequency of occurrence is in direct proportion to the amount of probing carried out in manipulating the catheter and to the excitability of the myocardium. Other complications include conduction defects, syncopal episodes, air embolism, venospasm, pyrogenic reactions, and trauma to the endocardium. The latter, a frequent complication in animals,[6] is rare in man. Since the procedure entails some risk to the patient, a committee was established by the Scientific Council of the American Heart Association [7] in order to evaluate the risk of both cardiac catheterization and angiocardiography and also to recommend methods to minimize the risks. The members of the committee were those with major experience in these techniques. Of 5691 catheterizations reported by the members, there were four deaths, a mortality of less than 0.1%. The report on angiocardiography revealed that in a hospital described by one of the committee members 1256 patients were studied by means of 2197 injections without a fatality. Yet, in a group of 6824 patients gathered from 182 centers by correspondence there were 26 deaths. It is probable that similar information would have been obtained had a large number of centers reported on their experience with cardiac catheterization. Since catheterization of the heart has come into wide popularity and the skill and experience of various manipulators varies, it is important that any new hazard be emphasized in the literature.

In 1951, McMichael and Mounsey [8] reported a characteristic syndrome which occurred in five patients subsequent to the "unrecognized entry of the catheter into a cardiac vein either via the coronary sinus or directly from the right atrium." In each case, the catheter tip was advanced to the "pulmonary out flow tract" but could not be advanced further. At this point, or a short time thereafter, the patients noted substernal pain with radiation between the shoulder blades. In one patient the pain also radiated into the neck, ears, and occiput. In all the patients, the heart rate either remained unchanged or became somewhat slower, despite signs of shock, which consisted of cold skin, cynosis, and a significant drop in blood pressure. Electrocardiograms in three of the patients revealed changes consistent with posterolateral myocardial ischemia, pericarditis, and a small anterolateral myocardial infarction, respectively. The electrocardiograms were unchanged in two patients. In one patient, a few milliliters of slightly blood-stained fluid was withdrawn through the catheter. It was assumed that the catheter had perforated a coronary vein and lay in the pericardium in this case. Another patient developed a pericardial friction rub. Fortunately, all the patients recovered after 10, 10,

Submitted for publication April 12, 1955.

From the Cardiovascular Section, Medical Service, McGuire Veterans Administration Hospital.

This study was supported by funds from the Research Division, Department of Medicine and Surgery, Veterans Administration, Washington, D. C.

3, 3, and 14 days, respectively, although the initial prognosis appeared grim in all but one patient. It was the opinion of these authors that occlusion of tributary veins of the coronary sinus, rather than of the sinus itself, resulted in these clinical findings. In view of the age of these patients, the authors imply that the changes described are more likely to occur in persons with coronary artery disease. In November, 1951, Smith and co-workers [9] described another patient who "became seriously ill following deep catheterization of the coronary veins." The patient was a 61-year-old man, who developed a syndrome identical with that described by McMichael and Mounsey, except for a much stormier course marked by shock, congestive heart failure, bronchopneumonia, pericarditis, fever, substernal pain, and electrocardiographic changes which persisted for two months. A subsequent case was reported by Stern and co-workers [10] in 1952. It is probable that this syndrome has occurred in many more cases in which the catheter was presumed to be in the outflow tract of the right ventricle.

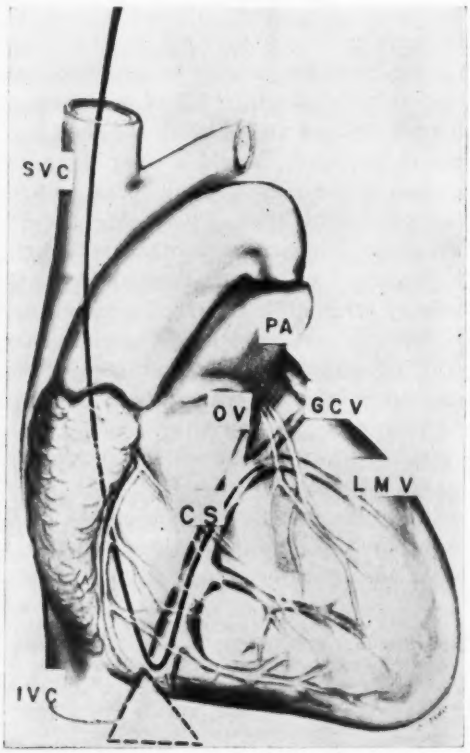


Fig. 1.—Anteroposterior view of the heart with a catheter resting in the coronary sinus and its tip about to enter the left marginal vein. The drawing attempts to depict a transparent heart in order that the coronary sinus can be visualized in relation to other structures of significance. *SVC*, superior vena cava; *PA*, pulmonary artery; *IVC*, inferior vena cava; *OV*, oblique vein of left atrium; *GCV*, great cardiac vein; *LMV*, left marginal vein, and *CS*, coronary sinus.

As a result of experience gained by deliberate catheterization of the coronary sinus for studying coronary blood flow and myocardial metabolism in approximately 40 patients, we have made certain observations which we consider of importance in the prevention of this syndrome. None of these patients has developed the characteristic syndrome previously described. In this respect, it should be noted that no difficulty has been reported with the catheter tip resting in the coronary sinus, and, in fact, valid studies of coronary blood flow and myocardial metabolism cannot be carried out if the coronary venous system is obstructed.

The method followed in attempting a deliberate catheterization of the coronary sinus consists first in turning the supine patient into the right anterior oblique position. After the catheter is passed into the inferior vena cava, it is gradually withdrawn, with the tip directed toward right ventricle. The patient is then instructed to take a deep breath and to hold it. One can then detect a triangular area of decreased density with its base at the diaphragm and its apex at the AV sulcus bordered by the inferior vena cava on the left and the ventricle on the right (Fig. 1). In most cases, the orifice of the coronary sinus will be situated just above the apex of this artificial triangle. The catheter is then withdrawn from the inferior vena cava and carefully advanced. Should its tip successfully impinge in the coronary sinus orifice, a rhythmical vertical, or up and down, motion will be imparted to the catheter. Should the catheter enter the ventricle, rhythmical horizontal motions of much greater vigor will be imparted. As the catheter is advanced, it forms an acute angle at the point where it enters the coronary sinus orifice (Fig. 2*B*).

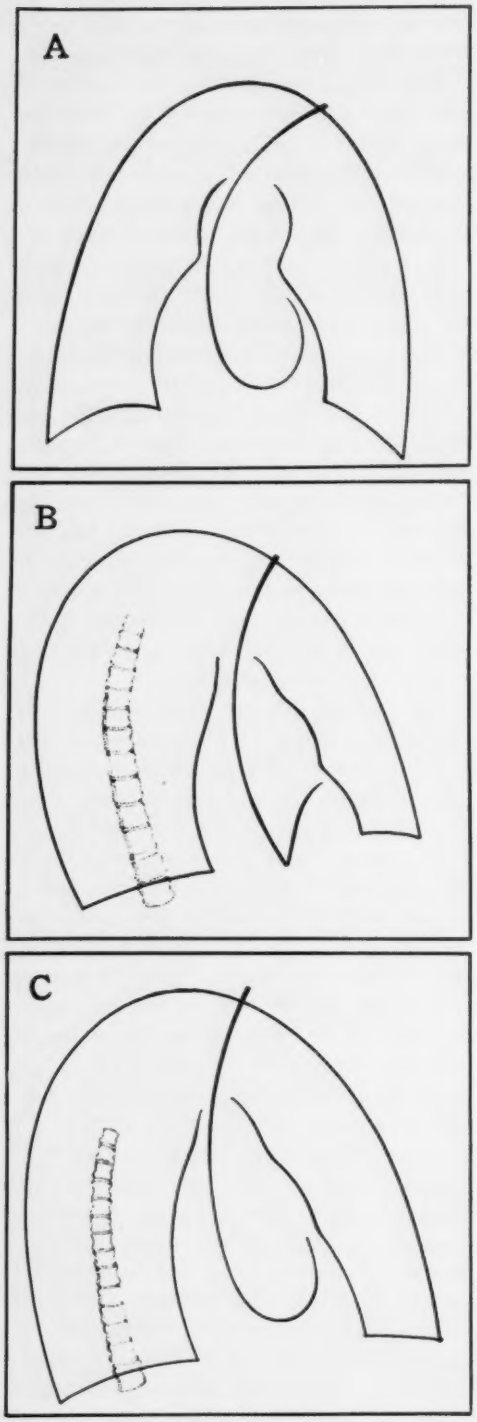
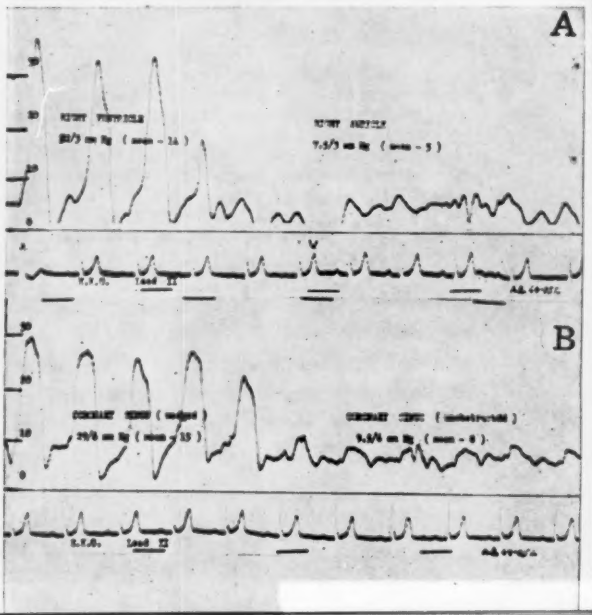


FIGURE 2

Fig. 2.—*A*, anteroposterior view of catheter which may be resting in either the right ventricle or coronary sinus; *B*, right anterior oblique view with catheter in the coronary sinus; *C*, right anterior oblique view with catheter in the right ventricle.

Such angulation may be seen in the anteroposterior view but is usually not so marked. Should the catheter enter the right ventricle, however, it will assume the form of a half loop (see Fig. 2*C*). The importance of this variation is obvious, since in the anteroposterior view the catheter usually observes the same configuration whether it is in the coronary sinus or in the right ventricle (Fig. 2*A*). Should the catheter be advanced into the left marginal vein, it will be seen to curve toward the apex and to follow the outer border of the heart. Should it enter the great cardiac vein, however, it will appear to pass into the outflow tract of the right ventricle, the main pulmonary artery, and behind the heart, into what appears to be the left pulmonary artery. If a Cournand type catheter is used, the pressure tracing obtained may tend to confirm one's impression that the catheter is indeed in the outflow tract of the right ventricle, as seen in Figure 3*B*. This is in contrast to the right ventricular pressure in the same patient (Fig. 3*A*). Withdrawal of the catheter into the unobstructed coronary sinus in the first instance or into the right auricle in the second instance reveals

Fig. 3.—*A*, pull-back pressure tracing from right ventricle to right auricle; *B*, pull-back pressure tracing from obstructed coronary sinus (actually coronary vein) into unobstructed coronary sinus.



similar pressure tracings, except that the unobstructed coronary sinus pressure is slightly higher than the right auricular pressure. Also, a definite C-wave seems to be lacking in the coronary sinus pressure curve. The A- and V-waves are prominent. The latter becomes especially conspicuous with the coronary vein obstructed. The position of the catheter after it is withdrawn from the coronary vein should suggest its location, but this may not always be the case. Unless one is quite familiar with the configuration of the coronary sinus pressure tracing, the differentiation depends primarily upon appearance of the catheter in the right anterior oblique view and on the oxygen content of the coronary venous blood as compared with that from the right auricle or right ventricle. The usual oxygen content of coronary sinus blood is about 5 vol. %, as compared with 12 to 15 vol. % in the right auricle or right ventricle. This difference is obvious to the eye.

COMMENT

In view of these observations, it has been our routine during catheterization of the heart to observe the following practice: In the event that any difficulty is obtained in passing the catheter from what appears to be the right ventricular outflow tract into the pulmonary artery, particularly if there seems to be an unusual absence of irritability and the catheter seems to loop rather low in the right auricle or right ventricle, the catheter is withdrawn about 2 cm. and the patient is rotated into the right anterior oblique position. The distinction should then become obvious. In order to obtain further support, blood from this area is compared with that obtained from the right auricle, as are the pressure tracings obtained. It is our opinion that the routine use of this procedure should reduce the incidence of the syndrome of occlusion of the coronary veins.

SUMMARY

A syndrome resembling myocardial infarction or acute pericarditis may occur following the unrecognized obstruction of a coronary vein during cardiac catheterization. In this instance, the catheter tip usually appears to have entered the outflow tract of the right ventricle but will not pass further. A routine is suggested based on our experience with deliberate catheterization of the coronary sinus, which should eliminate this potentially fatal syndrome. The differentiation is based on (*a*) the appearance of the catheter in the anteroposterior versus the right anterior oblique position, (*b*) the visible difference in oxygen content of coronary vein versus right atrial or right ventricular blood, and (*c*) the difference in pressure records obtained from these two sites.

REFERENCES

1. Forssmann, W.: Die Sonderung des rechten Herzens, Klin. Wchnschr. **8**:2085 (Nov. 5) 1929.

2. Klein, O.: Zur Bestimmung der zirkulatorischen Minutenvolumens beim Menschen nach dem Fickschen Prinzip, München med. Wchnschr. **77**: 1311 (Aug. 1) 1930.

3. Cournand, A., and Ranges, H. A.: Catheterization of Right Auricle in Man, Proc. Soc. Exper. Biol. & Med. **46**:462 (March) 1941.

4. Bing, R. J.; Vandham, L. D., and Gray, F. D., Jr.: Physiological Studies in Congenital Heart Disease: Results Obtained in 5 Cases of Eisenmenger's Complex, Bull. Johns Hopkins Hosp. **80**:323 (June) 1947.

5. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Seibel, R. S., and Evans, J. M.: Studies on Congenital Heart Disease: I. Techniques of Venous Catheterization as a Diagnostic Procedure, J. Clin Invest. **26**:547 (May) 1947.

6. Banfield, W. G.; Hackel, D. B., and Goodale, W. T.: Cardiac Lesions Following Venous Catheterization of the Right Auricle and Coronary Sinus of Dogs, J. Lab. & Clin. Med. **35**:287 (Feb.) 1950.

7. Cournand, A.; Bing, R. J.; Dexter, L.; Dotter, C.; Katz, L. N.; Warren, J. V., and Wood, E.: Report of Committee of Cardiac Catheterization and Angiocardiography of the American Heart Association, Circulation **7**:769 (May) 1953.

8. McMichael, J., and Mounsey, J. P. D.: A Complication Following Coronary Sinus and Cardiac Vein Catheterization in Man, Brit. Heart J. **13**:397 (July) 1951.

9. Smith, W. W.; Albert, R. E., and Rader, B.: Myocardial Damage Following Inadvertent Deep Cannulation of the Coronary Sinus During Right Heart Catheterization, Am. Heart J. **42**:661 (Nov.) 1951.

10. Stern, T. N.; Tacket, H. S., and Zachary, E. G.: Penetration into Pericardial Cavity During Cardiac Catheterization, Am. Heart J. **44**:448 (Sept.) 1952.

Loculated Interlobar Pleural Effusion Due to Congestive Heart Failure

Report of Five Cases

JOHN A. HIGGINS, M.D.
JOHN L. JUERGENS, M.D.
ANDRÉ J. BRUWER, M.D.
and
THOMAS W. PARKIN, M.D., Rochester, Minn.

In recent years the problem of cancer of the lung has been emphasized increasingly in the medical and lay press. Programs for mass x-ray surveys and the routine use of roentgenograms of the thorax as part of the physical examination have resulted in earlier detection of thoracic neoplasms, and improved surgical techniques have made the removal of these tumors more practicable. With this emphasis on the early detection and surgical removal of thoracic tumors, it seems appropriate to call attention to an uncommon and nonsurgical cause of a circumscribed density which may appear on the roentgenogram of the thorax.

A loculated pleural effusion within an interlobar fissure can be of various shapes and sizes and can produce a density simulating a tumor or other types of disease of the lung on the roentgenogram of the thorax. These interlobar pleural effusions may be due to congestive heart failure, and, if so, the effusion will usually disappear when cardiac compensation is restored. For this reason it has been referred to in the literature as a "vanishing tumor" of the lung. The criteria for a vanishing tumor of the lung which have been proposed by others [1] and which seem reasonable to us are (1) the appearance of a circumscribed interlobar density concomitantly with the signs or symptoms of congestive heart failure and (2) the disappearance of this shadow with the successful treatment of the cardiac decompensation.

Submitted for publication May 9, 1955.

Fellows in Medicine, Mayo Foundation (Drs. Higgins and Juergens); Section of Roentgenology (Dr. Bruwer) and Section of Medicine (Dr. Parkin), Mayo Clinic and Mayo Foundation. The Mayo Foundation is a part of the Graduate School of the University of Minnesota.

METHOD OF STUDY

The records of Mayo Clinic patients with roentgenologic evidence of interlobar pleural effusion were reviewed. A total of 188 such records had been filed by the Section of Roentgenology during the 10-year period 1945 through 1954. Although the etiologic factors producing these effusions were many and varied, it is of interest that 36 of the 188 patients (19.1%) had interlobar effusion at a time when they also suffered from congestive heart failure and had no other discernible cause for pleural effusion. However, only five cases completely satisfied the diagnostic criteria for a "vanishing tumor" of the lung. The remaining 31 cases were rejected from this study either because the interlobar effusion failed to clear completely with treatment or because follow-up roentgenograms were not taken to verify the total disappearance of the loculated fluid. Brief reports of the five cases follow.

REPORT OF CASES

CASE 1.—A 50-year-old man was referred to a thoracic surgical service at the Mayo Clinic in June, 1945, because of a "tumor of the right upper lung," discovered by his home physician on a roentgenogram of the thorax. His chief complaint was exertional dyspnea of three months' duration. Physical examination showed auricular fibrillation and an apical diastolic murmur along with other auscultatory evidence of mitral stenosis and distention of the veins of the neck. A roentgenogram of the thorax revealed an oval density in the right transverse fissure and moderate cardiac enlargement (Fig. 1*a* and *b*). Treatment with digitalis and re-

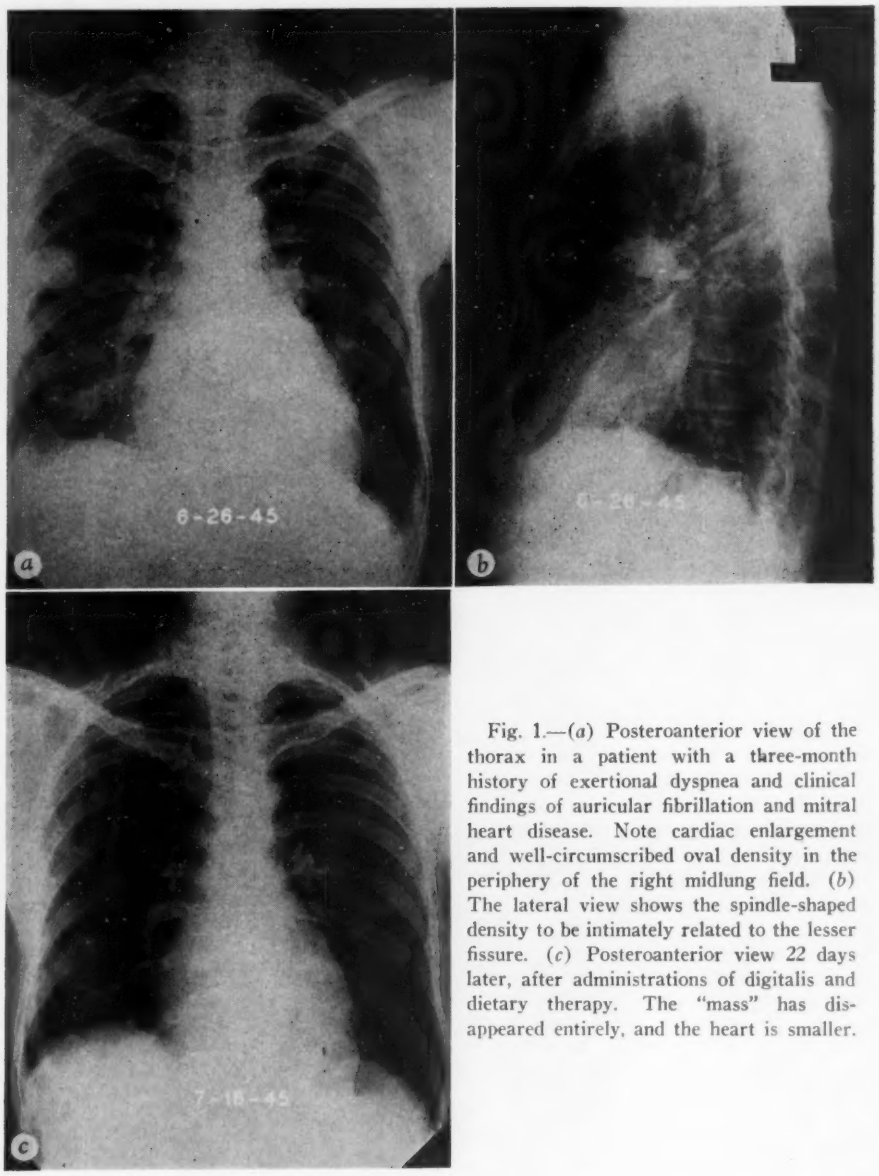


Fig. 1.—(*a*) Posteroanterior view of the thorax in a patient with a three-month history of exertional dyspnea and clinical findings of auricular fibrillation and mitral heart disease. Note cardiac enlargement and well-circumscribed oval density in the periphery of the right midlung field. (*b*) The lateral view shows the spindle-shaped density to be intimately related to the lesser fissure. (*c*) Posteroanterior view 22 days later, after administrations of digitalis and dietary therapy. The "mass" has disappeared entirely, and the heart is smaller.

stricted use of salt in the diet produced excellent results, and the patient lost 10 lb. rather promptly. A roentgenogram of the thorax (Fig. 1*c*) taken 22 days after initiation of treatment showed complete disappearance of the supposed tumor.

CASE 2.—A 53-year-old woman was admitted to St. Marys Hospital (Rochester) in December, 1949, for treatment of hemiplegia on the right side due to cerebral arterial thrombosis. She had a three-year history of recurrent exertional dyspnea and edema of the ankles. On physical examination the patient was dyspneic; moist rales were heard in both lung bases, and an enlarged liver was palpable. A roentgenogram of the thorax (Fig. 2*a*) showed evidence of cardiomegaly and loculated fluid in the right transverse and the right oblique fissures. A diagnosis was made of congestive heart failure due to sclerosis of the coronary arteries. Routine treatment resulted in an excellent clinical response, and a roentgenogram of the thorax (Fig. 2*b*) taken four days after initiation of treatment revealed evidence of old scars caused by pleuritis in both costophrenic

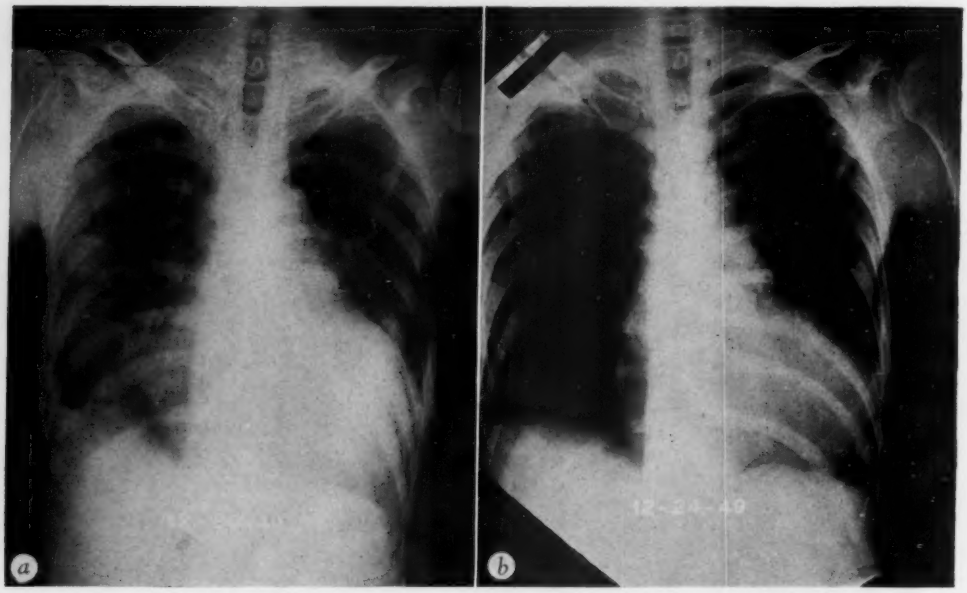


Fig. 2.—(*a*) Anteroposterior roentgenogram taken by means of a portable x-ray unit showing cardiac enlargement, an oval density in the region of the periphery of the lesser fissure, and evidence of an effusion in the oblique fissure. (*b*) Posteroanterior view taken four days after view shown in (*a*). The patient had demonstrated excellent clinical response to medical therapy. The effusions have been completely absorbed.

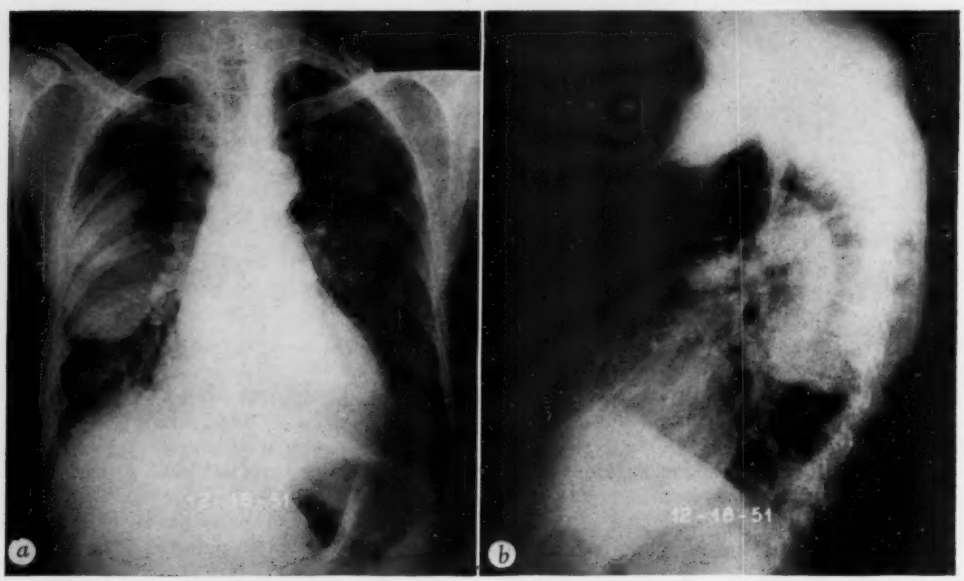


Fig. 3.—A spindle-shaped effusion is evident in the right oblique fissure and extends slightly into the lesser fissure. Also note the loculated effusion between the parietal and peripheral pleurae against the right posterior thoracic wall.

angles but complete disappearance of the interlobar effusion.

CASE 3.—A 69-year-old retired farmer was hospitalized in December, 1951, complaining of nervousness and mild exertional dyspnea. Definite evidence of congestive heart failure was lacking at that time. Although a history of syphilitic infection could not be obtained, serologic tests for syphilis revealed strongly positive results. Roentgenograms of the thorax taken on Dec. 18, 1951, showed one circumscribed density in the right oblique fissure extending a short distance into the lesser fissure and another against the right posterior thoracic wall (Fig. 3*a* and *b*). Subsequently, increasingly severe dyspnea and orthopnea developed along with the signs of aortic valvular insufficiency. A diagnosis was made of congestive heart failure due to syphilitic aortic valvular insufficiency. Digitalization was carried out, and mercurial diuretics were administered. Roentgenograms of the thorax taken Dec. 28, 1952, showed disappearance of the loculated fluid (Fig. 4*a* and *b*). This patient has been hospitalized several times subsequently for treatment of recurrent heart failure. Each time cardiac decompensation recurred, the interlobar fluid reappeared.

CASE 4.—An 86-year-old man was first seen at the Mayo Clinic in April, 1954. He related a five-year history of recurring exertional dyspnea and orthopnea and was admitted to the Worrall Hospital (Rochester). He had been hospitalized on three occasions elsewhere for treatment of congestive heart failure. Our examination revealed an enlarged heart, an apical systolic murmur, and fluoroscopic evidence of an enlarged left atrium. A diagnosis of congestive heart failure due to mitral valvular insufficiency was made. Roentgenograms of the thorax revealed collections of fluid in both the right transverse and the right oblique interlobar fissures (Fig. 5a). Response to digitalis and diuretics was excellent, and roentgenograms of the thorax taken four days after treatment was started showed complete disappearance of the loculated fluid (Fig. 5*b*).

CASE 5.—A 69-year-old retired farmer was admitted to the Worrall Hospital (Rochester) in September, 1954, for evaluation of a "spot on the right lung." He complained of orthopnea, paroxysmal nocturnal dyspnea, and nocturnal cough which had been present for three months. Physical examination revealed distention of the veins of the neck, rales in the bases of both lungs, an enlarged liver, and cardiomegaly. A roentgenogram of the thorax showed an interlobar effusion in the right transverse fissure and two loculated effusions in the right oblique fissures (Fig. 6*a* and *b*). Restriction of salt and administration of digitalis and mercurial diuretics produced an excellent clinical response. Another roentgenogram of the thorax made on the fourth day of treatment demonstrated complete

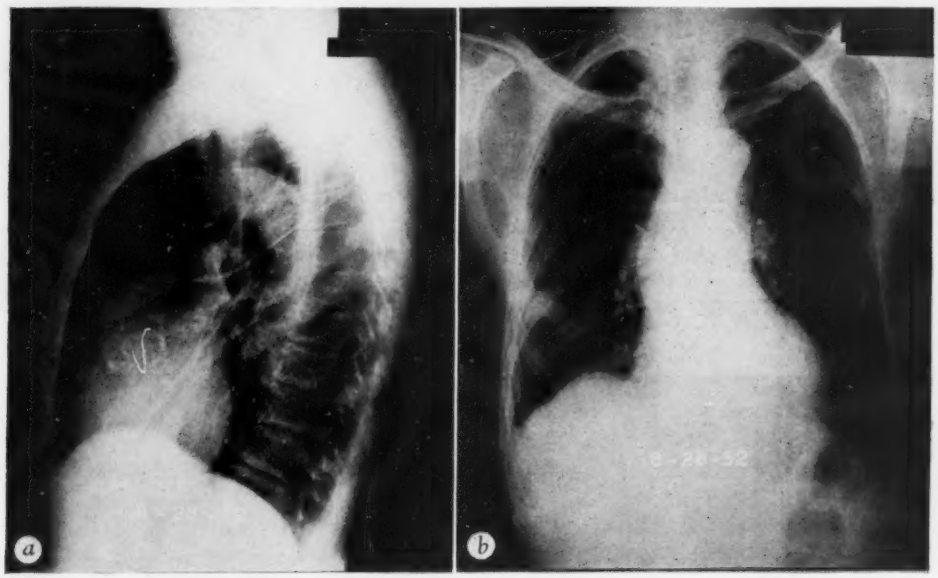


Fig. 4.—Posteroanterior and right lateral views of the thorax taken eight months after Figure 3*a* and *b*, during a period of cardiac compensation. The effusion in the oblique and lesser fissure has disappeared, only a slight thickening of these fissures being evident. The posterior loculated effusion has almost disappeared, a trace being evident on the posteroanterior view. Note also marked evidence of syphilitic aortitis.

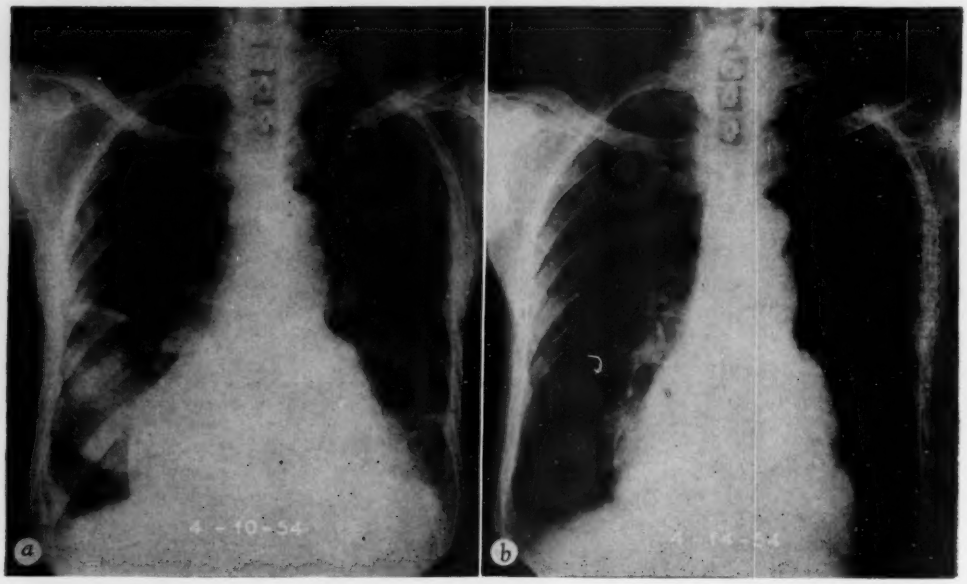


Fig. 5.—(*a*) Posteroanterior view of thorax shows small effusion in lesser fissure and larger loculated effusion in right oblique fissure. Note also cardiac enlargement and small effusion in left pleural space. (*b*) View taken four days later, after excellent response to medical therapy; effusion has disappeared and the size of the heart decreased slightly.

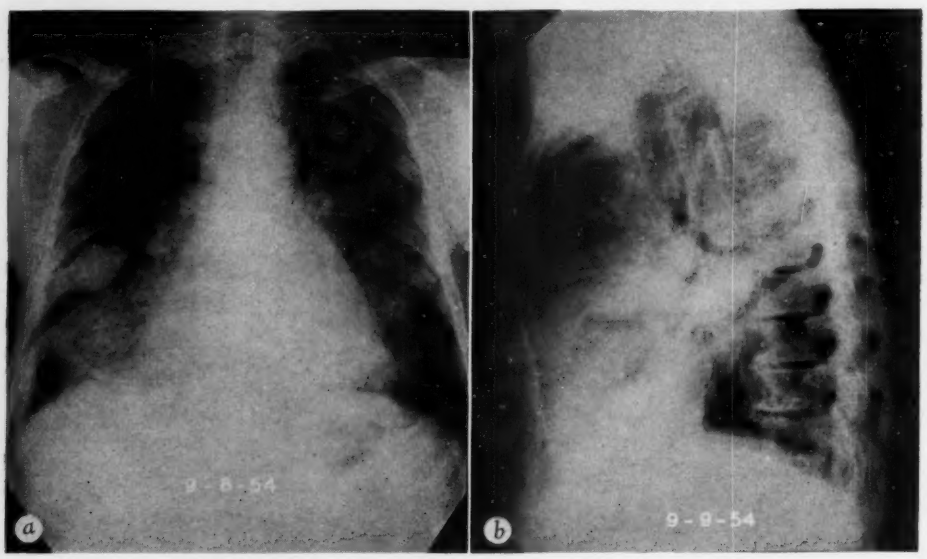


Fig. 6.—Posteroanterior and right lateral views of thorax taken on consecutive days, showing three separate spindle-shaped effusions, one in the lesser fissure and two in the right oblique fissure.

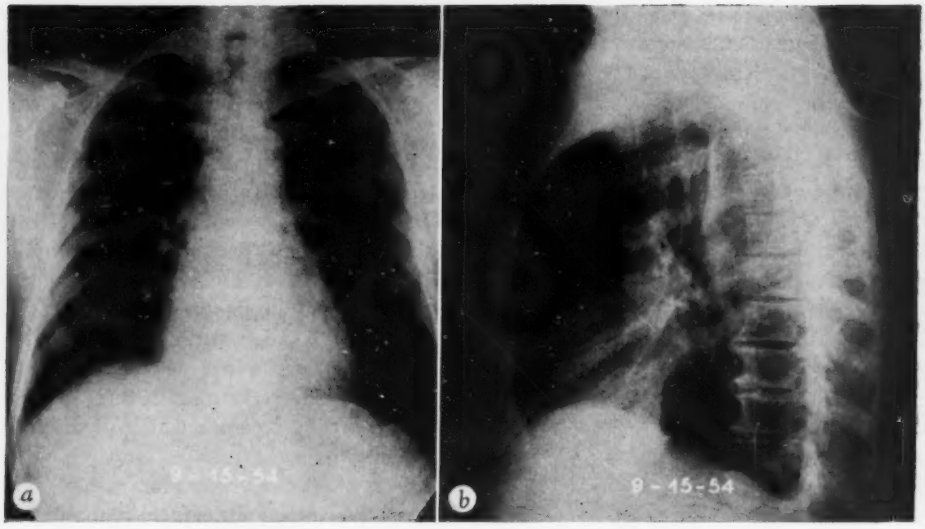


Fig. 7.—Views taken six days after those in Figure 6*b*, and four days after medical treatment for cardiac decompensation. The "tumors" have vanished. Note also decrease in size of heart.

disappearance of the interlobar fluid (Fig. 7*a* and *b*). A positive etiologic basis for the patient's cardiac failure was not established during his hospitalization.

COMMENT

At the time of our study, 63 cases of interlobar effusion among patients with congestive heart failure have come to our attention.* We have carefully reviewed these 63 reports, applying the criteria we have referred to previously. Those cases were discarded in which the interlobar effusion seemed to be merely an extension of a large free pleural effusion in the base of one lung. Some cases were rejected because a roentgenogram of the thorax was not obtained after treatment for congestive heart failure. Others were discarded if a roentgenogram of the thorax taken after treatment for heart failure revealed incomplete disappearance of the effusion. Those effusions not clearly attributable to heart failure alone, as, for example, interlobar effusions in patients with cardiac decompensation who also had an associated pulmonary infarction in the region, were not tabulated. Thus, by strict application of the criteria mentioned, the number of well-defined, authentic cases of vanishing tumor has been reduced to 36.† These 36 cases, together with the 5 we are reporting, bring the total of well-documented cases reported in the literature to 41.

TABLE 1.—*Location of Interlobar Pleural Effusion Due to Congestive Heart Failure*

Site	Reported in Literature	Present Series
Right transverse fissure	25	1
Right transverse fissure and right oblique fissures	3	3
Right oblique fissure	3	1
Left oblique fissure	3	..
Azygous fissure	2	..
Total	36	5

Analysis of the 41 cases shows that in 26 (63.4%) the effusions were located in the right transverse fissure alone and that in another six cases (14.6%) the site of effusion was in the right transverse and right oblique fissures (Table 1). Thus, the transverse fissure was involved in 78% of cases. One of the reasons for this preponderance may be that loculated effusions at this site are more readily discovered on the routine roentgenograms showing posteroanterior

* References 1-25.

† References 1-22.

views of the thorax, since the rays pass through the greatest diameter of the mass of the effusion. Effusions in the oblique fissure on either side are best seen on lateral views and, therefore, are more likely to be overlooked and remain unreported when only posteroanterior views are examined. An anomalous azygous lobe is a rather uncommon occurrence, and an effusion into the azygous fissure would be expected to be rare.

The etiology of the congestive heart failure responsible for the interlobar pleural effusion is varied (Table 2). In 11 cases (about 25%) the terms "coronary artery disease" or "arteriosclerotic heart disease" were used by the authors in describing the cause of the heart failure.

TABLE 2.—*Etiology of Congestive Heart Failure in Interlobar Pleural Effusion*

Etiology	Reported in Literature	Present Series
Coronary artery disease	3	1
Arteriosclerotic heart disease	7	..
Hypertensive heart disease	7	..
Hypertensive heart disease and arteriosclerotic heart disease	2	..
Rheumatic valvular disease	5	1
Syphilitic aortic valvular insufficiency	2	1
Thyrotoxic heart disease	1	..
Not stated or unknown	9	2
Total	36	5

The patients ranged in age from 30 to 86 years, with an average age of 55.2 years. More than half (57.5%) of the patients were in the sixth and seventh decades of life when the vanishing tumor was first discovered. Of the 35 patients whose sex was definitely stated, 31 (88.6%) were men and only 4 (11.4%) were women.

It is the opinion of most authors that a loculated interlobar effusion occurs when obliterative pleuritis makes the remainder of the pleural space unavailable for the accumulation of fluid. That this is not always the case is proved by reports in the literature [14] illustrating the occurrence of a free pleural effusion subsequent to the appearance of a collection of fluid in the interlobar spaces. Only rarely do these patients give a history of pleurisy. Repeated accumulations of pleural fluid are thought by some authors ‡ to play an etiologic role in some cases by producing an obliterative pleuritis.

Necropsy had been performed in six cases reported in the literature,§ and in all of these an obliterative pleuritis between the parietal and visceral pleural surfaces was demonstrated. Necropsy has not been performed on any of the five patients in our series.‖

It is of interest to note that in some of our cases and in many of those cases reported in the literature the predominant symptoms were of a type ordinarily associated with left ventricular failure. It seems to be generally recognized that pleural effusions usually are associated with the clinical picture of right ventricular failure. The reason for such a difference in the location of the effusion has been thought by some authors ¶ to be based on the belief that the visceral pleura which lines the interlobar spaces is drained by the pulmonary venous system while the parietal pleura is drained by the systemic venous system. Thus, increased pressure in the pulmonary venous system brought about by failure of the left ventricle is more likely to produce an interlobar effusion than is failure of the right ventricle with engorgement of the systemic venous system and impairment of drainage of the free pleural space. However, the exact cause for such an accumulation of fluid in the interlobar spaces has not yet been fully ascertained.

We think it is important to comment on the fact that two of our patients (Cases 1 and 5) were referred to the clinic because of possible tumors of the lung and that in another case (Case 3) a diagnostic biopsy was considered. It is obvious that exploratory thoracotomy in these patients is contraindicated. Since the degree of cardiac decompensation responsible for the interlobar effusion may be mild, the diagnosis of "vanishing tumor" of the lung is not always apparent initially, and the physician should

‡ References 7 and 26.

§ References 2, 4, 5, 10, and 21.

‖ See addendum.

¶ References 24 and 27.

keep in mind such a possible cause of a circumscribed density on the roentgenogram of the thorax.

ADDENDUM

Since the completion of this report, the patient described in Case 3 was again hospitalized with congestive heart failure. He failed to respond to treatment and died. Necropsy revealed the pleura of the right lung to be 0.5 cm. in thickness, with several regions of encapsulated fluid containing an estimated amount of 500 cc. Firm, fibrous adhesions obliterated the upper half of the right pleural space; adhesions also were present anteriorly on the left side. A free pleural effusion of approximately 1,500 cc. of straw-colored fluid was present on the left. There was anatomic evidence of marked syphilitic aortitis, with dilatation of the aorta and aortic valvular insufficiency.

REFERENCES

1. Gefter, W. I.; Boucot, K., and Marshall, E. W.: Localized Interlobar Effusion in Congestive Heart Failure: Vanishing Tumor of the Lung, Circulation **2**:336-343 (Sept.) 1950.

2. Stewart, H. J.: Pleural Effusion Localized in an Interlobar Space: Report of a Case of Heart Failure Together with Autopsy, Am. Heart J. **4**:227-235 (Dec.) 1928.

3. Kiser, E. F.: Pleural Effusion Associated with Congestive Heart Failure Localized in an Interlobar Space, Am. Heart J. **4**:481-483 (April) 1929.

4. Steele, J. M.: A Report of 2 Cases of Localized Pleural Effusion in Heart Failure, Am. Heart J. **7**:212-222 (Dec.) 1931.

5. Austrian, C. R.: Encapsulated Hydrothorax (Hydrothorax Saccatus Interlobaris) in Association with Myocardial Insufficiency, in Contributions of the Medical Sciences in Honor of Dr. Emanuel Libman by His Pupils, Friends and Colleagues, New York, The International Press, 1932, Vol. 1, pp. 101-112.

6. Vesell, H.: Interlobar Pleural Effusion in Heart Failure, M. J. & Rec. **135**:576-578 (June 15) 1932.

7. Stein, I. D., and Schwedel, J. B.: Interlobar Effusions in Patients with Heart Disease, Am. Heart J. **10**:230-239 (Dec.) 1934.

8. Stivelman, B. P.: Interlobar Pleural Effusions, Am. J. Roentgenol. **34**:475-481 (Oct.) 1935.

9. Shiflett, E. L.: Localized Pleural Effusion Accompanying Congestive Heart Failure: Report of 2 Cases, Radiology **25**:429-432 (Oct.) 1935.

10. Levitin, J.: Interlobar Effusion Associated with Heart Failure, Radiology **29**:190-193 (Aug.) 1937.

11. Pendergrass, E. P., and Neuhauser, E. B. D.: Pleural Lesions in Hemophilia: Report of a Case, Am. J. Roentgenol. **48**:147-151 (Aug.) 1942.

12. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, Ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943, pp. 230-231.

13. Boharas, S., and Criep, L. H.: Interlobar Effusion Associated with Congestive Heart Failure, Ann. Int. Med. **23**:426-431 (Sept.) 1945.

14. Laufer, S. T.: Interlobar Effusion Associated with Heart Failure, Nova Scotia M. Bull. **25**:229-234, 1946.

15. DiMaio, M.: Multiple Localized Pleural Effusions as a Manifestation of Congestive Heart Failure: Report of a Case, New England J. Med. **238**:502-506 (April 8) 1948.

16. Robertson, R. F.: Interlobar Hydrothorax in Cardiac Failure, Brit. Heart J. **13**:112-114, 1951.

17. Feldman, D. J.: Localized Interlobar Pleural Effusion in Heart Failure, J. A. M. A. **146**:1408-1409 (Aug. 11) 1951.

18. Newman, W., and Jacobson, H. G.: Bizarre Pulmonary Roentgenographic Manifestations in Heart Disease, Am. Heart J. **42**:184-193 (Aug.) 1951.

19. Behr, T. S.: Vanishing Tumor of the Lung: Report of a Case, M. Bull. St. Louis Univ. **4**:37-39 (Feb.) 1952.

20. Friedman, R. L.: Loculated Azygos Fissure Effusion in Cardiac Failure, Ann. Int. Med. **38**:582-585 (March) 1953.

21. Weiss, W.; Boucot, K. R., and Gefter, W. I.: Localized Interlobar Effusion in Congestive Heart Failure, Ann. Int. Med. **38**:1177-1186 (June) 1953.

22. Klosk, E.; Bernstein, A.; Simon, F., and Joelson, R. H.: Roentgen Diagnosis of Atypical Pleural Effusion Complicating Congestive Heart Failure, Tr. Am. Coll. Cardiol. **3**:128-139 (March) 1954.

23. Freedman, E.: Roentgenological Appearance of Interlobar and Mediastinal Encapsulated Effusion in the Thorax, Radiology **16**:14-29 (Jan.) 1931.

24. Bedford, D. E., and Lovibond, J. L.: Hydrothorax in Heart Failure, Brit. Heart J. **3**:93-111, 1941.

25. Russakoff, A. H., and Weinberg, T.: Encapsulated Pleural Effusion Due to Heart Failure: A Report of 2 Cases, New England J. Med. **230**:379-381 (March 30) 1944.

26. Rigler, L. G.: A Roentgen Study of the Mode of the Development of Encapsulated Interlobar Effusions, J. Thoracic Surg. **5**:295-305 (Feb.) 1936.

27. Miller, W. S.: The Lung, Springfield, Ill., Charles C Thomas, Publisher, 1937, pp. 69-83.

Studies on Urinary Lipase

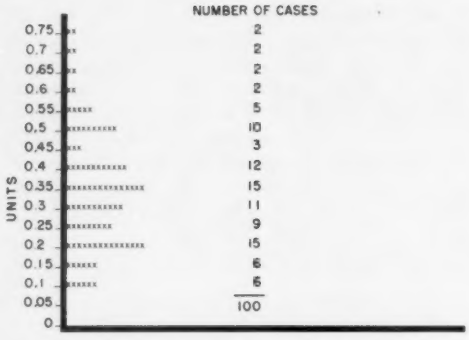
II. Urinary Lipase in Man

MARTIN M. NOTHMAN, M.D.
JOSEPH H. PRATT, M.D.
and
ALLAN D. CALLOW, M.D., Boston

In the first paper of this series[1] we showed that a fat-splitting enzyme is present regularly in the urine of dogs. In addition, we presented evidence that the fat-splitting enzyme is of pancreatic origin. Our conclusion is based on the following findings:

1. Injection of mecholyl and secretin increases the amount of fat-splitting enzyme in the urine. 2. Removal of the pancreas causes an immediate disappearance of the enzyme in the urine. 3. Ligation of the pancreatic ducts leads to a marked rise in the excreted amount of the enzyme followed slowly by a decrease to rather low levels. 4. Pancreatectomy is followed by the disappearance of the fat-splitting enzyme from the urine. 5. Ligation of the ducts followed by pancreatectomy causes an immediate disappearance of the high values of the enzyme in the urine.

These experimental findings formed the basis for studies on urinary lipase in man. The purpose of the present investigation was to determine the values for lipase in the urine of a large number of healthy persons under a variety of physiological conditions. Material for analysis represented samples of urine from members of the International Ladies Garment Workers' Union, collected at the occasion of their annual health examination. The determinations were performed according to the method described in the first paper of this series. The result of the test is presented in the Figure.



Values for lipase (units per cubic centimeter) in the urine of normal persons.

A study of 100 persons revealed an average of 0.35 units per cubic centimeter of urine, with a range of 0.1 to 0.75 units. This means that after incubation of the urine-oil emulsion mixture for 24 hours between 0.1 cc. and 0.75 cc. of N/20 NaOH have been necessary for the titration of the liberated fatty acids to a pink end-point with phenolphthalein. Among those 100 values, 75 were between 0.2 and 0.5 unit. Twelve were lower than 0.2 unit; 13 were higher than 0.5 unit. Only two reached the highest values, of 0.75 unit. Values of 1.0 unit and more are considered to be significant increases.

Determinations of urinary lipase in the same person during the day and on some consecutive days do not show any considerable differences. The values observed in an individual person, determined three times daily for seven days, ranged between 0.2 and 0.45 units; in another one, between 0.35 and 0.55 units. Determination of urinary lipase in one

Submitted for publication May 20, 1955.

From the Medical and Surgical Departments of the New England Medical Center and Tufts University Medical School.

Supported by a grant-in-aid from the American Cancer Society upon recommendation of the Committee on Growth of the National Research Council.

person 10 times in 24 hours showed 0.5 unit as the highest value and 0.25 unit as the lowest value.

Fasting apparently has no influence on the concentration of the lipase excreted in the urine, nor has the intake of a rich meal. After 24 hours of fasting the urinary lipase was still 0.35 unit, as it has been before. Two, four, and six hours after a meal rich in fat and proteins the values for urinary lipase were 0.2, 0.3, and 0.25 unit, respectively. Determination of the urinary lipase concentration during a glucose-tolerance test shows only small change of the values.

Although the values for the concentration of lipase in the urine differ only insignificantly in specimens taken during the day, these small changes are apparently great enough to maintain a daily output which does not vary much from one day to another. In 25 cases the total 24-hour volume of urine was collected and the total amount of urinary lipase was determined. The Table shows the result. The diagnosis in most of these patients was psychoneurosis; others were patients for whom minor surgery had to be performed.

Total Amount of Urinary Lipase Excreted in Twenty-Four Hours

	Volume of Urine in 24 Hr., Cc.	Urinary Lipase, Units/Cc.	Total Output of Lipase in the Urine, Units
1	1200	0.4	480
2	1800	0.35	630
3	1400	0.35	630
4	1280	0.5	640
5	2280	0.15	342
6	650	0.45	292
7	520	0.45	234
8	360	0.6	216
9	1800	0.3	540
10	2520	0.15	378
11	1810	0.1	181
12	1020	0.2	204
13	1400	0.35	490
14	2140	0.1	214
15	1740	0.3	522
16	1350	0.15	202
17	650	0.6	390
18	1190	0.45	535
19	1100	0.25	275
20	1970	0.3	591
21	2200	0.35	770
22	800	0.5	400
23	1540	0.5	770
24	1210	0.65	780
25	1820	0.35	637

The volume of urine secreted in 24 hours varied between 360 cc. and 2520 cc.; the total output of urinary lipase ranged from 180 to 780 units. The highest volume of urine did not show the lowest concentration of urinary lipase, and the highest concentration of urinary lipase was not excreted with the smallest amount of urine. But, still, the total amount of excreted urinary lipase did not exceed 800 units in 24 hours and went below 200 units only in a single case.

In those patients in whom the total amounts of urinary lipase were determined on several consecutive days the daily variations were even smaller. Here is one characteristic example: In four consecutive days amounts of 292, 254, 429, and 215 units, respectively, were excreted from one person.

In 12 cases of pregnancy, ranging from the third month to the seventh month, the values for urinary lipase were determined to be from 0.1 to 0.75 unit. In these cases the urinary diastase was determined at the same time. It was always found to be normal, as it was also in women who showed renal glycosuria of pregnancy.

From the data presented we conclude that in the urine of normal persons a fat-splitting enzyme is regularly present in a concentration ranging from 0.1 to 0.75 unit. This range equals the range determined in the serum of normal persons, where, also, values from 0.1 to 0.7 unit are found and where, according to our experience, values above 1.0 cc. measured with N/20 sodium hydroxide solution have to be considered as pathologic.[2] Neither fasting nor the intake of large amounts of food causes any significant change in the concentration of excreted lipase. Furthermore, we believe the conclusion to be warranted that the variation in the total amount of excreted urinary lipase in 24 hours in consecutive days is small in the same person. In different persons the variations are somewhat greater, ranging from 200 to 800 units but never exceeding this amount.

SUMMARY

In 100 cases of healthy persons a fat-splitting enzyme could be regularly detected in the urine. The value for the urinary lipase ranges from 0.1 to 0.75 unit, the average being 0.35 unit. Among those 100 values 75 were between 0.2 and 0.5 unit.

The variations in the same person during one day and on consecutive days are small.

Fasting and food have no significant influence on the concentration of lipase in the urine.

The 24-hour output of lipase in the urine in 25 persons ranged from 200 to 800 units. The daily variations are rather small.

REFERENCES

1. Nothman, M. M.; Pratt, J. H., and Callow, A. D.: Studies on Urinary Lipase: I. On a Fat-Splitting Enzyme in Urine and Its Relations to Pancreas, A. M. A. Arch. Int. Med. **95**:224-230, 1955.

2. Nothman, M. M.: The Value of Functional Tests for the Diagnosis of Diseases of the Pancreas, Ann. Int. Med. **34**:1358-1371, 1951.

Tuberculous Pleurisy with Effusion

J. ARTHUR MYERS, M.D., Minneapolis

PATHOGENESIS

When tubercle bacilli invade the body by any portal of entry they are ingested by neutrophiles, many of which enter the blood stream and are soon focalized in various places. More focalizations occur in the lungs than in any other organ. Lemon and Montgomery [1] found that when tubercle bacilli are placed into pleural spaces of normal rabbits they are soon phagocytosed and some are deposited in lymph nodes and remote organs. Others have observed that when tubercle bacilli are introduced subcutaneously or directly into the stomach or intestines, many may soon be found in the lungs and elsewhere about the body where they have been focalized. Tubercles are formed at the points of focalization and may harbor bacilli for long periods. At any point of focalization where bacilli remain alive they may at a subsequent time be liberated and disseminated to immediate and remote areas.

Inasmuch as many primary focalizations are in the lungs and often are located subpleurally, it is to be expected that some will result in pleural involvement just as when such focalizations occur in the brain some will liberate tubercle bacilli into ventricles or directly into the subarachnoid space, resulting in meningitis. Miller [2] demonstrated that lymph from the immediate subpleural area of the lungs flows into the pleural lymph channels and from there toward the hilum. Thus from subpleural tubercles bacilli may be carried into the pleural channels, where lesions may result and produce pleural effusion. Again, subpleural tubercles may extend into or through visceral pleura and liberate bacilli into the pleural space. This probably is the usual source of bacilli resulting in effusion. Stead and co-workers [3] found caseous tuberculous foci in the lung contiguous with the diseased pleura in 12 of 15 persons who were explored surgically within a few months after effusion occurred.

Tuberculous pleurisy with effusion is usually an allergic manifestation. When tubercle bacilli invade the body, tubercle formation begins at the various points of focalization within an hour. Although Dienes [4] has demonstrated by microscopical methods the presence of allergy within three or four days after tubercle formation begins, sensitivity usually does not reach a degree detectable by the characteristic tuberculin reaction for about three to seven weeks.

Tuberculoprotein is innocous to tissues that have not been sensitized to it. However, it is poisonous and destructive to sensitized tissues. When tubercle bacilli are introduced into unsensitized tissue the reaction is mild and nonspecific, but when they are placed in tissues sensitized to tuberculoprotein a specific acute inflammatory reaction occurs.

Paterson [5] could not produce immediate pleural effusion of demonstrable proportions by introducing virulent tubercle bacilli into pleural spaces of unsensitized animals. However, effusions occurred immediately when

Submitted for publication May 6, 1955.

From the Student Health Service, School of Public Health, and Department of Medicine, University of Minnesota.

Prepared with the aid of the H. Longstreet Taylor Foundation, established by the Minnesota Tuberculosis and Health Association.

Presented in part before Postgraduate Course, Clinica Antillas, Rio Piedras, Puerto Rico, March 14, 1955, and Wisconsin Chapter, American College of Chest Physicians, Milwaukee, May 1, 1955.

bacilli were placed in pleural spaces of those previously sensitized.

Lemon and Montgomery [1] placed virulent bovine tubercle bacilli into pleural spaces of unsensitized rabbits. An extremely slight inflammatory reaction occurred with very small effusion which disappeared in three or four days. Within 15 to 30 days the animals became sensitized, as manifested by the tuberculin reaction. Then large effusions appeared and increased in amount until the animals died from generalized tuberculosis.

Lemon and Feldman [6] found that tuberculin placed into the pleural space of sensitized animals produced no effusion. They believe this failure is due to "rapid absorption, to dilution and distribution of the inoculum spread over the large pleural surfaces and to the absence of particulate material." They are of the opinion that "a sensitized pleura and living bacilli in the pleural space are requisite factors in the production of experimental tuberculous pleural effusion."

Apparently all cases of tuberculous pleurisy with effusion originate from previously established tuberculous lesions, the majority of which are in the lungs. Others may arise from lesions in lymph nodes, such as those in the lower cervical region, the mediastinum, and the abdomen. Tuberculous lesions in the abdomen may lead to pleural effusion just as suppurative lesions in abdominal organs such as the appendix may result in empyema. It has been suggested that some cases may be due to pleural invasions by the blood stream. However, well-documented evidence is lacking.

Tuberculous lesions in the chest wall, including intercostal lymph nodes, vertebrae, ribs, and costal cartilages, may discharge tubercle bacilli into pleural spaces. For example, in one case in our series fluid kept forming much beyond the usual time. Later, fluid appeared in the contralateral pleural space. This condition kept recurring until lesions were found in the fifth and sixth costal cartilages. These feeding foci were removed surgically, and there has been no recurrence of effusion for the past six years.

TIME OF APPEARANCE IN RELATION TO ESTABLISHMENT OF ALLERGY

Pleurisy with effusion may occur soon after a high degree of allergy is established or at any subsequent time as long as allergy and living tubercle bacilli are present and free pleural space exists. A considerable number of our cases occurred in persons who were known to be nonreactors to tuberculin but who within a few weeks or months after exposure to cases of tuberculosis without adequate contagious disease technique were found to be reactors; pleurisy followed fairly promptly. In others, pleurisy with effusion was the first manifestation that infection had occurred, as it appeared between the regular testing intervals. However, in all cases, when pleurisy with effusion was detected, the persons reacted characteristically to tuberculin.

Tuberculous pleurisy with effusion may make its first appearance many years after primary infection is acquired. For example, a man of 70 years who at the age of 20 had been successfully treated for pulmonary tuberculosis had remained entirely well for 50 years when he developed excruciating chest pain followed by demonstrable effusion. A physician who had a bout with primary tuberculosis as a medical student in 1892 later completed the medical course and conducted a general medical practice the remainder of his life. In later years x-ray films revealed residuals of the old lesions in the form of calcific deposits. However, in 1944, at the age of 80 years, he experienced sudden excruciating pain over the right lower axilla and 2,000 cc. of clear straw-colored fluid containing tubercle bacilli were aspirated. After a brief convalescence he resumed general practice, and he died from coronary disease at the age of 87 years.

Apparently tuberculous pleurisy with effusion occurs more frequently in young children who are invaded with tubercle bacilli than is generally believed. If pain is present it may not be recognized by others, and unless adequate examination is made the fluid absorbs without being diagnosed. The youngest child in our group was one

year old. She was first examined, in 1929, because her father was found to have contagious tuberculosis. She reacted to tuberculin, and primary infiltration was present in the left upper lobe. A few weeks later she had massive effusion in the left pleural space. The fluid absorbed and calcium was deposited in the lesions of the primary complex, both in the left upper lobe and in the left hilum region.

Pleural changes such as obliteration of costophrenic angles suggesting residuals of effusions in children with no history of past illness that would account for such conditions lead one to suspect that they existed but were not detected. We have found these more frequently among reactors than among nonreactors to tuberculin.[7] For example, they were seen in 1.73% of 5968 nonreactors and in 3.06% of 4377 reactors, all children.

There is considerable evidence that pleurisy with effusion occurs in adults much more frequently than is generally believed. Many persons do not consult physicians unless pain and other symptoms are severe or persist. In many cases symptoms are of short duration and fluid absorbs promptly and no examination is made. Others are examined and the fluid is not found. Still others are diagnosed as having pneumonia, influenza, neuralgia, neuritis, etc., without adequate examination.

OBSERVATION

Practically every disease that attacks the lungs, mediastinum, and chest wall may result in accumulation of pleural fluid. This is also true of some conditions immediately above the thorax and in the abdomen. Our observations, which began in 1920, have been mainly on groups of school children, university and nursing school students, and persons of various ages in chest clinics and private practice. They include many persons with pleural fluids due to malignant disease including Hodgkins disease, benign tumors, brucellosis, chylothorax, hemothorax from injury, abdominal and pelvic surgery, rheumatic fever, clinical pulmonary tuberculosis, empyema, cardiac conditions, acute pulmonary infections, etc. There were 37 with demonstrable pleural fluid whose examinations were not complete enough to justify etiological diagnoses. These were persons who appeared in clinics, etc., but did not return.

This report is limited to 260 persons who had at least clinical diagnosis of tuberculous pleurisy with effusion in the absence of demonstrable reinfection type of pulmonary disease when effusion appeared. This condition is sometimes spoken of as primary. However, it is secondary, since it is preceded and produced by primary lesions.

Diagnosis.—More cases of tuberculous pleurisy with effusion are seen by physicians in general practice than by those engaged in special phases of medicine. This is because the great majority of infected persons at any given time are apparently in good health. However, they are potential cases of pleurisy with effusion. The onset is often acute and sudden, and, if medical consultation is sought, the family physician is the first to make the examination.

TABLE 1.—*Age Distribution*

Age, Yr.	Cases, No.
0- 4	4
5- 9	5
10-14	15
15-19	29
20-24	95
25-29	65
30-34	19
35-39	10
40 and over	18
Total	260

All 260 persons in this group were examined personally. Some were not seen during the attack of pleural effusion but later came under our care for various reasons, mainly periodic examinations. In such cases, previous records were procured in order that the information be adequately documented. A considerable number were seen in consultation with other physicians, and subsequent information was obtained from them. They ranged from 1 to 80 years old (Table 1). One hundred thirty-nine were females. Effusions appeared on the right side in 141.

The most frequent type of onset consisted of pain in an axilla of persons who apparently were in good health. Pain varied from mild ache to that which was excruciating. Usually this was followed fairly promptly by elevation of body temperature, which in some cases reached 103 or 104 F. A few gave no history of having had pain and fever. This has been observed by others, including Chadwick,[8] who emphasized the importance of absence of history of pain in pleural effusions in children. For example, in one group of 8838 children who had routine x-ray film inspection, he found effusion in 12 in whom it was not previously suspected. In another group, of 2100 children from 3 to 17 years of age, routine x-ray films revealed effusion in 46.

When pain is present one should not be deceived by its disappearance. Complete relief may be experienced after hours or a few days, owing to separation of the visceral and parietal pleurae by accumulation of fluid.

The physician is hard pressed to make a diagnosis of tuberculous pleurisy with effusion in the absence of characteristic tuberculin reaction. All of our cases reacted characteristically to tuberculin.

In the beginning, conventional physical examination usually is unrevealing except for splinting of the diaphragm and chest wall due to the reflex protective mechanism. Pleural friction rubs of dry pleural crackles are heard in some cases. As fluid accumulates in sizable amount the percussion note becomes flat and egophony may be elicited immediately above the fluid.

Fluoroscopic and x-ray film inspections are of great value, although they may be unrevealing for a few days or longer after the initial pain is experienced. Rigler * has shown that less than 300 cc. of fluid in a pleural space is not revealed by ordinary fluoroscopic inspection or the usual posteroanterior roentgenogram. However, in lateral decubitus position as little as 100 cc. may be detected. Therefore, when pleural effusion is suspected by reason of symptomatic onset and no abnormality is seen more than splinting of the diaphragm and other secondary evidences, roentgen inspection should be repeated every day or so, with use of the lateral decubitus position if necessary.

Subsidance of pain, together with failure to repeat roentgen inspection, may account for failure to make accurate diagnosis or its delay for weeks or months. In a few of our cases several months elapsed after the acute onset of symptoms before fluid was discovered. For example, one woman was examined in several medical centers in Europe and America over a period of four months before a large effusion was detected. Where she was first examined the roentgenogram showed no evidence of fluid. This history of fairly recent "negative chest" misled subsequent examiners, who did not repeat roentgen inspection. All persons included in this report presented roentgen-ray evidence of fluid.

Neglecting to examine adequately when persons report with suggestive symptoms is a common cause of postponement or even failure to diagnose the condition. One man in this group had reported to several centers over a period of weeks because of chest pain and later increasing shortness of breath, without being examined. It was not until he had a temperature of 104 F that roentgen inspection was made, after which 1500 cc. of fluid was aspirated.

Recovery of tubercle bacilli is the only incontrovertible finding in the diagnosis of tuberculous pleural effusion. While clear straw-colored fluid is suggestive in a tuberculin reactor, there are other diseases which result in such fluid.

Sixty-eight of the patients in this series were not aspirated and therefore had no bacteriological studies. Some of the reasons for this failure are as follows: 1. When these observations began it was generally believed that practically all cases of so-called idiopathic pleurisy with effusion (that is, those without etiology such as pneumonia, malignant disease, and the like) were due to tuberculosis. Therefore, diagnosis was thought justifiable without specific evidence.

* References 9 and 10.

2. Many physicians feared aspiration because of the possibility of introducing pyogenic micro-organisms. In those days mixed infection empyemas produced in tuberculous pleural spaces were exceedingly serious. There was no antimicrobial drug to help cope with them. With surgical drainage, with or without extrapleural thoracoplasty, there was the possibility of persisting pleurocutaneous sinuses. 3. Some patients refused aspiration.

Tubercle bacilli were not found or no laboratory report was available in 116 who were aspirated. Probably some of these cases were not tuberculous, although they reacted to tuberculin. Particularly in the earlier years of these observations, the medical profession regarded nearly all cases of "idiopathic" pleurisy with effusion as tuberculous. Stead and co-workers [3] explored surgically 24 cases within a few months aftter acute effusion. All 24 were presumed to have tuberculous pleurisy and were being so treated. However, nine proved to be nontuberculous. Our failure to recover bacilli in those that were tuberculous may have been due in part to small amounts of fluid sent to laboratories. For many years, when fluid was aspirated it was limited to 5 to 10 cc. Such amounts were not dependable. It was not unusual to restrict bacteriological study to stained smears. Later in these observations the importance of procuring large volumes of fluid when possible was recognized. Moreover, sediment should always be cultured and, preferably, animals should be inoculated. It seems likely that when these examinations are made routine such expressions as "idiopathic" and "consider tuberculous until proved otherwise" may be heard less frequently. When tubercle bacilli are not found, one may now resort to pleural biopsy or more extensive surgical exploration to determine etiology. In some cases this will avoid a long course of treatment and even compensation for tuberculosis which does not exist.

Tubercle bacilli were recovered in 76 of this series.

Treatment.—When these observations began, 35 years ago, there was already considerable enthusiasm for bed rest in treatment of tuberculosis. Therefore it was usually recommended that persons with tuberculous effusion be on strict bed rest for at least several months at home or in a sanatorium. This was not always accepted. Thus bed rest in this group of patients has ranged from none to more than two years in sanatoriums. The majority had from three to six months of bed rest.

It was thought that accumulations of pleural effusion represented Nature's attempt to rest the underlying lung so as to promote healing of subpleural lesions. Therefore it was thought unwise to remove fluid unless toxemia persisted unduly long or pressure symptoms developed. This accounts in part for the 68 in this group who were not aspirated.

Localized rest had already gained prominence in the treatment of pulmonary lesions; thus, removal of fluid and replacement of air became a popular form of treatment. This maintained the splinting of the lung which nature had instituted with fluid. Pneumothorax was continued for approximately the same period as for clinical pulmonary tuberculosis. This was employed in a sizable number of our patients, both in and out of sanatoriums.

It was learned that fluid allowed to remain in a pleural cavity often results in deposits of fibrin on both the visceral and parietal pleural surfaces to such extent as to cause them to appear thickened, with obliteration of costophrenic angles. Occasionally extensive fibrothorax or calcification ocurred, markedly reducing pulmonary function. Many physicians then began to aspirate as much fluid as possible as fast as it accumulated in order to prevent fibrin accumulations.

In this series of cases, only 94 cleared so as to leave no residual on x-ray film inspection. This does not necessarily mean that fibrin deposits are not still present. In the remainder pleural changes have persisted so as to cast x-ray shadows. These changes vary from slight blunting of costophrenic

angles to complete obliteration of angles with elevation and partial immobilization of diaphragms. In a few cases there are pleural changes visible above the diaphragm. Stead and co-workers [3] found fibrous peel more than 1 cm. thick surrounding the lung in 13 of 15 persons explored surgically within a few months after acute effusion had been present.

It is not known to what degree fibrin later absorbs without organization. In some of our cases there has been remarkable clearing of x-ray shadows over the years. It seems likely that these residuals might have been prevented if frequent aspirations had been done or might have been removed in the more extensive cases, if decortication had been available within a few months after they were in evidence.

Regardless of the method of treatment employed or its absence, all persons in this series made good recovery from the immediate illness.

Obviously many persons with tuberculous pleurisy with effusion are not diagnosed for lack of examination, and no treatment is administered. Others refuse or do not follow prescribed treatment. With this form of tuberculosis, like others, including pulmonary disease, many persons recover without treatment. Therefore there are now excellent physicians who believe that fluid should not be removed except in small amounts for diagnosis unless it becomes massive enough to cause pressure symptoms, toxemia persists unduly long, or empyema develops.

However, there are enough cases in which complications occur as a direct result of the effusion, such as marked pleural changes, or subsequent tuberculous conditions evolve to justify prompt and adequate treatment of all persons found to have effusion. Inasmuch as the disease is controlled spontaneously in so many, it is difficult to evaluate any form of treatment. Antimicrobial drugs have not been in use sufficiently long and experience with them has not been large enough to justify conclusions.

We now believe that persons with tuberculous pleurisy with effusion should have the fluid removed and the pleural space kept as dry as possible thereafter, that the usual antimicrobial drugs in the same combinations and dosage as used in pulmonary tuberculosis should be administered, that strict bed rest should be prescribed for six months or longer if the condition warrants, and that graduated exercise be employed leading to restoration of working capacity during the next six months. Only time will tell whether antimicrobial drugs are effective enough to reduce the period of bed rest and graduated exercise. When cases are first seen after fluid has been present for weeks and there is evidence of fibrin deposits, decortication should be considered in order to prevent permanent residuals.

If present or future chemotherapy proves effective in destroying all tubercle bacilli in the bodies of recent converters to the tuberculin reaction, it may be possible to cure tuberculosis, including pleurisy with effusion, if it appears soon after the tissues have become sensitized. The only criterion of cure will be reconversion of the tuberculin reaction.

Prognosis.—The immediate prognosis in uncomplicated pleurisy with effusion is good. Apparently the remote prognosis differs little if at all from that of persons who have no evidence of tuberculosis except characteristic sensitivity to tuberculin. Sizable groups of children and young adults have been followed over considerable periods after they became reactors to tuberculin, and an appreciable number have been observed to develop clinical lesions in peripheral lymph nodes, meninges, lungs, bones, joints, and other organs whether or not pleural effusion intervened.† In fact, the majority of such cases did not have pleural effusion. Among the students of medicine, University of Minnesota, graduating in the classes of 1930 to 1951, inclusive, 963 became infected while in school or subsequently. Pleurisy with effusion occurred in 20, of whom 4 later had clinical tuberculosis. There were 25 of the 963 who developed clinical tuberculosis, in 4 of whom pleural effusion had intervened.[11]

† References 7 and 11.

It is the underlying cause and not pleural effusion which determines remote prognosis. This underlying cause is the foci of tubercle bacilli deposited in various parts of the body promptly after the initial invasion occurs. All of them may remain silent during a person's lifetime. On the other hand, at any time throughout the person's life after these foci are established one or more of them may provide bacilli for reinfection type of lesions. Subpleural ones may cause pleural effusion, those in the central nervous system may cause meningitis, and so on, with all acute and chronic clinical lesions.

There is diversity of opinion regarding remote prognosis. This may be due in part to groups of patients reported. For example, if only persons with clinical tuberculosis who give histories of having had pleurisy with effusion some years before are considered, conclusions can be misleading. In the areas from which these persons originated there may have been several others who had undiagnosed effusions or were treated successfully, with no later tuberculous lesions.

Inclusion of demonstrable primary pulmonary infiltrates as clinical pulmonary disease can be deceiving. Except for those who have chest wall lesions and the like, all persons with pleural effusion have antecedent primary infiltrates. However, relatively few are large enough, have adequate consistency, or are so located as to be visualized on x-ray films. From x-ray shadows alone it is impossible to determine whether lesions are primary infiltrates or reinfection clinical disease. This differentiation can be made only when periodic tuberculin testing has been done or by subsequent observation of the lesions.[12] Shadow-casting primary infiltrates in any part of the lungs may be obscured from view when fluid is present and first be observed after it has absorbed or is aspirated. Even then, some such infiltrates are not visualized until they later have sufficient consistency to obstruct x-rays. In my experience, primary infiltrates per se in children or adults rarely become significant clinically. In the present series of cases, 55 presented pulmonary shadow-casting lesions while fluid was present or soon after, which proved to be primary infiltrates. None subsequently became clinical. Five were later treated because slight x-ray changes were thought to have occurred.

It is not unusual for interlobar fluid or fluid loculated anteriorly or posteriorly to be mistaken for pulmonary lesions from the x-ray shadows it casts. This also applies to fibrin deposits with or without fibrosis.

In the 260 persons included in this report pleurisy was the first manifestation of tuberculosis, except in those who had previously reacted to tuberculin and 2 who had tuberculous cervical lymphadenitis in childhood. All were apparently in good general health when pleurisy appeared. None had evidence of clinical pulmonary disease.

TABLE 2.—*Deaths*

Cases, No.	Cause of Death	Years from Effusion to Death
3	Coronary thrombosis	17, 19, 21
3	Accidents	8, 18, 25
2	Tumors	18, 29
1	Suicide	23
1	Diphtheria	1
1	Otitis media	8
Total 11		187

SUBSEQUENT DEVELOPMENTS

For this study 247 of the 260 have been traced, and health information, including recent examinations, has been brought to date. Eleven have died from nontuberculous conditions with no clinical tuberculosis intervening (Table 2).

Deducting the 11 deaths, there remain 236 whose tuberculosis status is known. The years that have elapsed since pleural effusion occurred are shown in Table 3. This amounts to 4620 total number of person-years of follow-up.

Only the following patients have developed conditions for which treatment was administered:

One had pleural effusion at the age of 19 years, in 1917. Bacilli were recovered from fluid. Artificial pneumothorax was later instituted. Although he worked regularly, he did not make satisfactory recovery until decortication was done, in 1951.

Primary Lesions.—One with primary infiltrate in evidence when effusion appeared was treated in a hospital for one year, and the infiltrate was resected. Bacilli were not recovered from fluid. He has remained well for the successive three years.

One had right pleural effusion when she was 24 years old. Fluid was not aspirated, but she was on bed rest for 18 months. A primary infiltrate was in evidence. When she was 48 years old effusion recurred on the right side, but bacilli were not found. The primary focus had remained unchanged.

TABLE 3.—*Follow-Up Data*

Years Followed	Cases, No.	Cases with Later Lesions, No.	Years Followed	Cases, No.	Cases with Later Lesions, No.
1	1	..	21	8	..
2	5	2	22	9	1
3	3	..	23	7	..
4	1	1	24	12	..
5	2	..	25	14	1
6	3	1	26	11	..
7	5	1	28	5	..
8	5	..	29	8	1
9	9	1	30	7	1
10	11	2	31	3	1
11	7	..	32	4	1
12	6	1	33	4	1
13	6	..	34	2	..
14	11	1	35	3	..
15	11	..	36	2	..
16	7	..	37	3	..
17	10	4	38	1	..
18	4	..	39	1	..
19	10	1	45	1	..
20	6	1	50	1	..

She was in a sanatorium 11 months for effusion. She has remained well through the subsequent 12 years.

One with tubercle bacilli found in fluid presented a primary infiltrate. Eleven years later there were slight x-ray changes around the primary focus but there were no clinical manifestations. The focus was resected. She has remained well during the three succeeding years.

One with bacilli found in fluid at age 21 had a demonstrable primary infiltrate. When she was 36 years old x-ray changes were found in the region of the primary focus. Following thoracoplasty she has remained well over the succeeding 16 years.

One at the age of 20 years had effusion which was not aspirated. A primary infiltrate was demonstrated. When she was 22 years old there were slight x-ray changes in the region of the primary focus. She was hospitalized for 17 months, but lesions showed no clinical manifestation. She has been well for the past 18 years.

One at the age of 28 years had bacilli found in fluid and a primary pulmonary infiltrate was in evidence. Three years later there were slight x-ray changes in the region of the primary focus. She received antimicrobial drugs for six months and has been well for the succeeding four years.

Extrathoracic Lesions.—Three developed skeletal lesions. One of them had a tuberculous costal cartilage with cold abscess, which appeared seven years after the pleural effusion. This was removed 17 years ago, and she has since been well. Another at age 64 had effusion on the left side in 1940 and on the right side in 1944. Bacilli were recovered from both sides. He was not relieved from trouble on the right side until the fifth and sixth costal cartilages were found to be tuberculous and removed, when he was 73 years old. During the six subsequent years he has remained well. The third was 22 years old when effusion appeared on the left side. Aspiration was not done. Four years later the right cuneiform bone was removed and proved to be tuberculous. He has remained well during the intervening 22 years.

A woman was 28 years old when effusion from which bacilli were recovered appeared, in 1948. She had pelvic symptoms in 1954. Tuberculosis was not suspected, but surgery revealed this disease in the uterus, uterine tubes, and one ovary, which were removed.

A girl of 15 years had pleural effusion in 1924. Bacilli were not found in the fluid. When she was 8 years old she had enlarged left cervical nodes diagnosed as tuberculous, but they subsided without drainage or treatment. In 1931 x-ray film inspection of her neck revealed evidence of calcium deposits in these nodes. In 1938 these lesions became reactivated and were removed. During the past three or four years she has had an occasional "spot" on the left leg which usually healed only after x-ray treatment. Recent

biopsy of one currently present revealed papulonecrotic tuberculid. She is now receiving isoniazid. Since 1924 her work and usual activities have been interrupted only when the cervical lymph nodes were removed.

A woman had effusion in 1928, when she was 28 years old. Fluid was not aspirated. Two years later she died from tuberculous meningitis and generalized miliary disease.

A woman of 28 years in 1937 had pleural effusion. Bacilli were not found in the fluid. In 1939 she died in a sanatorium, from tuberculous peritonitis.

A woman 24 years old in 1949 had effusion from which bacilli were recovered. She was treated in a sanatorium for one year. In 1953 tuberculous peritonitis was present and she was hospitalized for 17 months.

A woman of 19 years in 1926 was treated for pleural effusion. Bacilli were not recovered from the fluid. In 1928 she had tuberculous peritonitis treated by bed rest and pneumoperitoneum. No evidence of clinical disease has appeared in the past 27 years.

At the age of 13 years in 1918 a boy had pleural effusion. Tubercle bacilli were recovered. He was on strict bed rest for a few months. Thereafter he remained well until 1930, when right nephrectomy was done for tuberculosis. He has since had no evidence of clinical tuberculosis.

Reinfection Type of Pulmonary Tuberculosis.—Thirteen patients later developed clinical pulmonary lesions. One of these occurred one year after the effusion and was treated successfully. One had tuberculous pneumonia one year after effusion and died from pulmonary hemorrhage three years later.

One had a pulmonary lesion appear two years after effusion and was treated successfully 20 years ago.

Four years after effusion three developed pulmonary tuberculosis. In one the pulmonary lesion appeared in 1949 and was resected in 1954. Her gastric washings still yield tubercle bacilli. Another who presented a pulmonary lesion in 1929 had 14 months of bed rest and has since been well. The third had effusion at the age of 23 years in 1938. Bacilli were recovered from the fluid. In 1942 a minimal lesion was treated in a sanatorium for four months. Reactivation occurred in 1948 when she was hospitalized for one year. She has since been well.

A man of 21 years had effusion in 1930. Bacilli were not found in the fluid. In 1935 shadow-casting lesions were present in the apex of each lung. No treatment was administered except a well-regulated life. These lesions never became clinical. He has been in good health since 1935.

A man of 26 years had pleural effusion in 1936. The fluid was not removed. In 1942 disease developed in the upper lobe of the left lung. He was admitted to a sanatorium, and extrapleural thoracoplasty was done. He has remained well.

A woman of 20 years had effusion in 1923. The fluid was not aspirated. In 1931 a lesion in the upper lobe of the left lung was treated by artificial pneumothorax. In 1938 a lesion appeared in the upper lobe of the right lung, which was treated successfully in a sanatorium. She has remained in good health.

A woman of 27 years had pleural effusion in 1922. Bacilli were not recovered. She remained in good health until 1936, when bilateral upper lobe lesions appeared. She had paraffin packs introduced during the two years she was in a sanatorium. There has been no further evidence of tuberculosis.

A woman of 21 years had pleural effusion in 1938. Tubercle bacilli were not found. In 1952 a small lesion appeared in the upper lobe of the left lung. She spent several months in a sanatorium, where the lesion slowly disappeared from x-ray view without producing symptoms.

A man of 51 years had effusion in 1935. No fluid was aspirated. In 1942 lesions were present in one lung and tubercle bacilli were found in the sputum. He made a good recovery but died from coronary thrombosis in 1952.

Thus, among 236 persons who had clinical diagnoses of pleurisy with effusion 5 were

later treated because of equivocal slight x-ray changes at the site of primary foci. None presented clinical manifestations. In three of these cases, the changes occurred within the first 3 years after the effusion; in two, 11 and 15 years later. The sixth had recurring pleural effusion 24 years after the initial attack, but the primary focus remained unchanged.

Twenty-three of our 236 cases subsequently developed reinfection type tuberculosis, and 10 of these had extrathoracic lesions. Of this number three of the lesions were in cartilage and bone, one in pelvic organs, one in kidney, and one in cervical lymph nodes and papulonecrotic tuberculids; one case was meningitis, and three were peritonitis. The patient with meningitis and one with peritonitis died.

Of the 10 with extrathoracic lesions, 2 had peritonitis and 1, meningitis two years after the effusion. One had a bone lesion and one had peritonitis four years after effusion. One had costal cartilages removed 5 years after effusion; one had pelvic disease 6 years after; one had costal cartilage lesions 7 years after; one had renal disease 12 years after, and one had cervical lymph nodes 14 years and papulonecrotic tuberculin 29 years after effusion.

Among the 13 who developed clinical pulmonary disease, 2 had demonstrable lesions within 1 year after effusion; 1, in 2 years; 3, in 4 years; 1, in 5 years; 1, in 6 years; 1, in 7 years; 1, in 8 years, also had a lesion appear in the contralateral lung in the 13th year; 1, in 13 years and 2 in 14 years after the effusion. Only two deaths occurred, both from nontuberculous conditions.

Among the 23 persons who subsequently developed clinical tuberculosis, 7 did not have pleural fluid aspirated. Of the 16 who were aspirated bacilli were found in 8.

Apparently primary infiltrates of sufficient size and consistency to cast x-ray shadows are not correlated with development of pleural effusion, since, among the 23 who developed reinfection forms of tuberculosis, in only 3 were there primary infiltrates at any time. Among 55 persons who had primary infiltrates in evidence about the time effusion was present, only 3 have since developed clinical tuberculosis.

Prevention.—Until recently, prevention of tuberculous pleurisy with effusion was entirely depedent upon avoidance of initial invasion with tubercle bacilli. Once the person was infected he was a potential case of pleurisy with effusion. This applied to all clinical forms of tuberculosis. Evidence is being adduced which strongly suggests that prompt antimicrobial drug treatment for recent converters may prevent meningitis. If these drugs will prevent central nervous system lesions and those adjacent to blood and large lymphatic vessels from eroding into brain ventricles, subarachnoid space, and blood stream, it seems possible that they may also prevent subpleural lesions from involving the pleura and causing pleurisy with effusion. This has not been determined.

SUMMARY AND CONCLUSIONS

Tuberculous pleurisy with effusion which occurs in persons who have no demonstrable clinical pulmonary tuberculosis is usually caused by subpleural lesions resulting from focalization of tubercle bacilli promptly after their first invasion.

With rare exceptions, pleurisy with effusion is an allergic phenomenon, the tissues having become sensitized to tuberculoprotein during the first three to seven weeks after the initial invasion occurs. Many effusions develop within a few months after allergy is established. However, they may appear decades later. They occur among tuberculin reactors of all ages from infancy through senility.

Apparently tuberculous pleurisy with effusion occurs more frequently than is generally believed, partially because of such factors as failure to examine for it.

This report includes 260 persons who had clinically diagnosed tuberculous pleurisy with effusion. None had demonstrable evidence of pulmonary reinfection type of tuberculosis when pleurisy appeared. All reacted to tuber-

culin, and all had 300 or more cubic centimeters of fluid which was demonstrable by x-ray film inspection.

Although recovery of tubercle bacilli is the only incontrovertible diagnostic criterion, they were found in only 76 of this group. In another 116 who were aspirated, organisms were not found. Sixty-eight were not aspirated. Reasons for these discrepancies are discussed in the text. It is now recommended that as much fluid as possible be removed and studied bacteriologically. If this fails, pleural biopsy or surgical exploration may be necessary to determine accurately whether long treatment or compensation for tuberculosis are justified.

All forms of treatment in vogue at the time these cases occurred were employed. It is now recommended that the pleural space be kept as dry as possible; that strict bed rest be employed at least six months, with graduated exercise for the succeeding six months, and that antimicrobial drugs be administered for at least one year following the day of diagnosis.

Treatment is directed not only to pleurisy but also to the underlying cause. All cases in this series regardless of method of treatment made good immediate recovery.

Remote prognosis depends upon existing conditions before pleurisy occurs rather than upon the effusion. Immediately after the initial invasion, tubercle bacilli are focalized not only in the lungs but in various other parts of the body. Any one or more such foci which continue to harbor tubercle bacilli may subsequently release organisms which result in clinical lesions. Pleurisy with effusion is only one of the numerous immediate and remote possibilities. It is doubtful that pleural effusion per se has any effect on subsequent developments, since large numbers of persons have been without intervention of effusion.

Of the 260 persons constituting this group, 247 (95%) were traced. Eleven had died from nontuberculous conditions, with no evidence of tuberculosis having developed. Twenty-three (9.7%) of the remaining 236 have developed reinfection clinical type of tuberculosis.

From these observations final conclusions cannot be drawn with reference to ultimate prognosis. Tuberculosis is a lifetime disease. There is still time in the majority of our cases for new lesions to appear and old ones to become reactivated.

There has been no method of preventing pleurisy with effusion after infection occurs. However, with antimicrobial drugs it may be possible to prevent effusion as well as all other clinical forms of tuberculosis if they are administered promptly after tuberculin conversion while lesions are small and vascular.

REFERENCES

1. Lemon, W. S., and Montgomery, L. G.: Pleural and Pulmonary Lesions Resulting from Intrapleural Injection into Rabbits of Mycobacterium Tuberculosis, J. Thoracic Surg. **3**:612, 1934.

2. Miller, W. S.: The Lung, Springfield, Ill., Charles C Thomas, Publisher, 1947.

3. Stead, W. W.; Eichenholtz, A., and Strauss, H. K.: Operative and Pathologic Findings in 24 Patients with Syndrome of Iodopathic Pleurisy with Effusion, Presumably Tuberculous, Am. Rev. Tuberc. **71**:473, 1955.

4. Dienes, L., and Mallory, T. B.: Histological Studies of Hypersensitive Reactions, Am. J. Path. **8**:689, 1932.

5. Paterson, R. C.: The Pleural Reaction to Inoculation with Tubercle Bacilli in Vaccinated and Normal Pigs, Am. Rev. Tuberc. **1**:353, 1917.

6. Lemon, W. S., and Feldman, W. H.: Experimental Tuberculous Pleural Effusion, Am. Rev. Tuberc. **48**:177, 1943.

7. Harrington, F. E.: The Evolution of Tuberculosis, Minneapolis Division of Public Health, 1944.

8. Chadwick, H. D.: The X-Ray and Clinical Diagnosis of Tuberculosis in Children, Am. Rev. Tuberc. **17**:318, 1928.

9. Rigler, L. G.: Roentgen Diagnosis of Small Pleural Effusions, J. A. M. A. **96**:104, 1931.

10. Rigler, L. G.: Roentgen Examination of the Chest, J. A. M. A. **142**:773, 1950.

11. Myers, J. A.; Diehl, H. S.; Boynton, E., and Horns, H. L.: Tuberculosis in Physicians: Chairman's Address, J. A. M. A. **158**:1, 1955.

12. Myers, J. A.: Primary Tuberculosis Acquired in Adulthood, Dis. Chest **22**:293, 1952.

Treatment in Internal Medicine

SENILE OSTEOPOROSIS

The Physiological Basis of Treatment

MARC MOLDAWER, M.D., Boston

OSTEOPOROSIS is as universal an alteration of aging bone as is osteoarthritis of aging joints. Together these comprise the main symptom-producing manifestations of skeletal senility. Although osteoporosis appears to be physiological in aging bone, its degree is very variable from person to person.

PATHOLOGICAL PHYSIOLOGY

Pathologically, osteoporotic bone is characterized by fewer and less thick trabeculae. Functionally such bone is more susceptible to compression and fracture, but until fracture occurs there is preservation of bone contour.

So far as is now known, there is no biochemical difference between the thin trabeculae and those of normal presenile bone; the protein matrix is the same, as is the bone salt, which is deposited in the matrix in an apatite crystal lattice. The ratio of minerals to matrix is probably the same in osteoporotic as in normal bone.

The skeleton is normally in a state of dynamic equilibrium, with bone resorption and bone production occurring constantly at different trabecular surfaces (Fig., left). Resorption of bone salt is a passive process, which occurs because the body fluids are undersaturated with respect to calcium and phosphorus, the main components of the bone salt. Concomitant with resorption of the bone salt the matrix in which it had been deposited disappears. Osteoclasts are an index of this process and are engaged in the removal of the matrix. Bone production is an active process: Osteoblasts manufacture matrix and the enzyme alkaline phosphatase, which increases the local concentration of phosphorus by its action on organic phosphates. The increased phosphorus concentration permits immediate precipitation of bone salt into the newly formed bone matrix. The number of osteoblasts is an index of the activity of bone production. The level of the serum alkaline phosphatase is a rough index of osteoblastic activity.

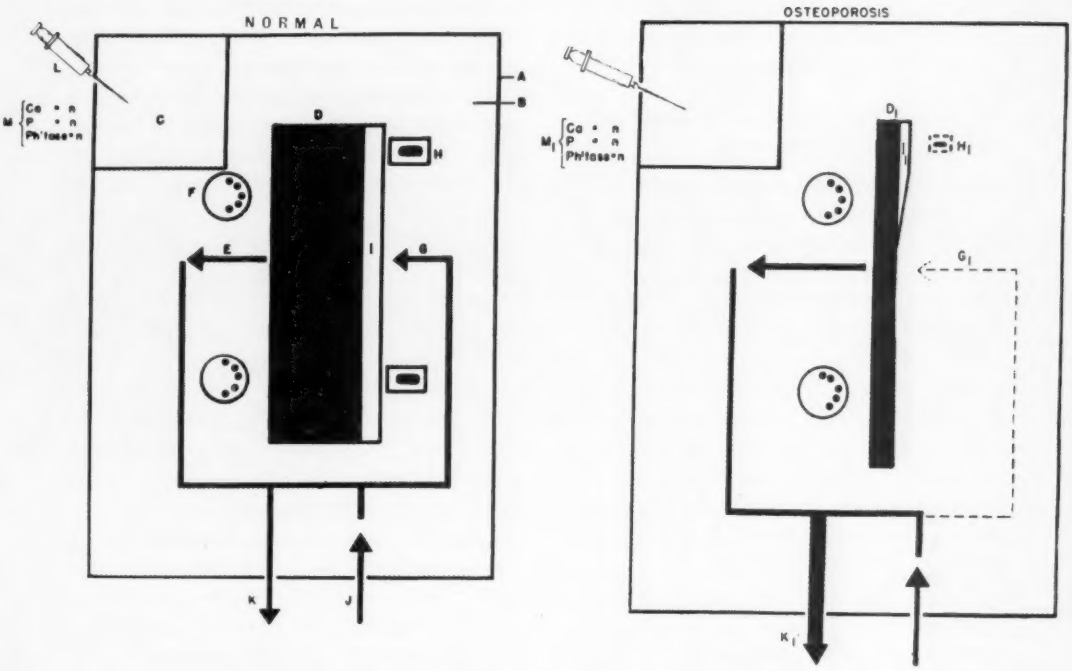
In osteoporosis (Fig., right) the serum levels of calcium and phosphorus are normal, and the rate of bone resorption is therefore assumed to be normal. The thin trabeculae, then, must be due to an underproduction of sufficient new bone to maintain normal balance. Histologically, the osteoblasts and osteoclasts appear qualitatively and quantitatively normal. The level of the serum alkaline phosphatase also tends to be normal in osteoporosis. Thus, proof that osteoporosis is due to decreased bone production rather than to increased bone resorption is not available histologically or chemically. It nonetheless appears to be the more logical cause of osteoporosis if it is agreed that resorption is a passive process, while production of bone is a more complicated active process.

The slowness with which senile osteoporosis develops suggests that the decrease in osteoblastic activity is exceedingly small relative to continuing bone production, and a decrease in osteoblasts would not be expected to be observable by routine histological study. Similarly, a decrease in alkaline phosphatase would not be anticipated.

With equilibrium of bone resorption and repair, the mineral content of the skeleton remains constant. The body is then in calcium equilibrium, as more than 99% of body

Submitted for publication May 2, 1955.

From Harvard Medical School and the Massachusetts General Hospital; Milton Research Fellow in Medicine.



Schematic diagrams to show conception of difference between normal bone and osteoporosis. *A*, body limits; *B*, body fluid; *C*, body serum, a compartment of body fluid easy to tap for analysis; *D*, bone mass with two surfaces, one where bone is being resorbed and one where it is being laid down; *E*, arrow indicating by its size rate of Ca and P resorption; *F*, osteoclast; G, rate of Ca and P deposition; *H*, osteoblast laying down *I*, osteoid; *J*, Ca and P entering body from gastrointestinal tract; *K*, Ca and P leaving body by kidney or other exits; *L*, syringe obtaining serum for analysis; *M*, blood values (n = normal; + = high; − = low). (From Albright, F., and Reifenstein, E. C., Jr.: The Parathyroid Glands and Metabolic Bone Disease, Baltimore, Williams & Wilkins Company, 1948.)

calcium is structurally associated with bone and teeth. In osteoporosis less calcium is redeposited in new bone matrix than is resorbed: there is a loss of calcium from the skeleton and the body is in negative calcium balance. The extra calcium is mainly excreted by the kidney, and the urine calcium tends to be elevated. Osteoporosis occurs gradually, and the increase in urine calcium may not be marked. Since the process tends to be self-limited, the urine calcium is often not high at the time that studies are made. The limiting factor in osteoporosis may be that the surface for passive resorption is decreased eventually to the point where resorption is equalled by bone production.

Phosphorus, unlike calcium, is present in large amounts in tissues other than bone; the urinary phosphorus is more dependent on dietary phosphorus than is the urine calcium on dietary calcium. Measurements of urinary phosphorus, without complete balance studies, are not informative. The considerations which apply to phosphorus also apply to nitrogen. Determination of urinary nitrogen and even nitrogen balance studies are of little help, since the amount of nitrogen loss from bone in the gradually occurring osteoporosis of old age is too small to be differentiated from nitrogen loss from other tissues.

Studies which are helpful in differentiating osteoporosis from other bone disturbances, therefore, are determinations of the serum calcium, phosphorus, and alkaline phosphatase, which are consistent with the diagnosis when they are normal. The alkaline phosphatase may be moderately elevated if there

has been a recent fracture. The urinary calcium is a rough index of the activity of the process, and it is usually elevated.

ETIOLOGICAL FACTORS IN SENILE OSTEOPOROSIS

The main stimulus to osteoblastic activity appears to be stresses and strains on bone which is constantly being weakened by resorption. In the immobilized person bone resorption continues normally while bone production decreases, leading to "osteoporosis of disuse." The decreased activity of many older persons lessens the stimulus of stress and strain to bone production but does not fully account for the changes observed. Undoubtedly a number of other factors are involved in normal osteoblastic stimulation, deficiencies of which are etiological factors in senile osteoporosis.

Perhaps foremost among these are changes occurring in the endocrine secretions concerned with bone metabolism. The frequently used term "postmenopausal osteoporosis," which can be considered as a special case of senile osteoporosis, emphasizes this etiological aspect, as it does the fact that osteoporosis is more frequently a pathological diagnosis in older women than in older men. Albright [1] has pictured the hormones of normal adults as being in equilibrium. On the one hand the adrenal S-hormone, being antianabolic, tends to decrease bone mass, while the combined anabolic action of the adrenal N-hormone, the ovarian estrogens, and the testicular androgens tends to counteract this effect. In the menopausal woman adrenal hormone production is probably decreasing, but estrogen almost entirely disappears, shifting the balance in favor of antianabolism. The rate and degree to which osteoporosis develops can in part be attributed to relative decreases in S and N hormones, which appear to differ from person to person. In the male the testes may continue to secrete androgens into far-advanced old age, but there is a progressive decrease in amount. Again the relative decrease in anabolic and antianabolic hormones determines the rate and degree to which osteoporotic changes ensue.

The role of other hormones is less evident at the present time. In both thyrotoxicosis and acromegaly osteoporosis is not uncommonly observed, although the hormones involved are ordinarily considered to be anabolic. It is possible that when dietary factors are inadequate for the accelerated rate of anabolism induced by these hormones, anabolism of other tissues occurs at the expense of bone. Whether thyroid and growth hormone are relatively excessive in old age is not known. In acromegaly estrogen can diminish the untoward effects of growth hormone, probably by suppression of the pituitary secretion of growth hormone rather than by peripheral antagonism. Conceivably growth hormone secretion increases in older persons with gonadal failure.

Other factors undoubtedly contribute to the senescence of bone. The diet of the older person often contains smaller amounts of protein, vitamins, and minerals than that of younger persons, but deficiencies are only rarely encountered in patients with senile osteoporosis. The decreased osteoblastic activity is not, therefore, due to dietary protein, vitamin, or mineral insufficiency, nor to abnormal absorption, although there may be as yet undetected qualitative deficiencies of amino acids or other nutrients. Deficiency of trace metals, for example, has been considered as a possible cause of senile osteoporosis, but there is no evidence to support this idea. Finally, the diminished blood supply to bone, secondary to arteriosclerosis, may also play a role in the decreased production of bone in aging persons.

SOME CLINICAL AND RADIOGRAPHIC ASPECTS OF SENILE OSTEOPOROSIS

Although osteoporosis is often apparent on radiographs taken for other reasons than complaint of bone pain, the diagnosis is characteristically entertained when an elderly person presents with complaint of back pain and when films show marked osteoporosis, often with evidence of recent vertebral fracture. The diagnosis should be considered in older patients with fracture of any bone, particularly when trauma has been minor. The high

incidence of wrist and hip fractures in the aged is undoubtedly due to osteoporosis, together with poor posture and poor musculature, which permits excessive strain to fall on weakened bone. Occasionally pain precedes fracture or other definite radiological evidence of osteoporosis.

Just as back pain is the most frequent complaint in patients with senile osteoporosis, so too the spine appears to be the first and most severely involved part of the skeleton roentgenographically. Next in order are the pelvis, ribs, and hips. Usually, when osteoporosis is evident in the long bones the spine is severely involved. It is difficult to be certain by radiographs when the skull is osteoporotic. The seemingly preferential order of osteoporosis by radiographs may be more apparent than real, insofar as thinness of bone trabeculae is concerned. Because the spine is more susceptible to pressures than other bones, there tend to be earlier alterations in vertebral contour, without which we are reluctant to make a diagnosis of osteoporosis. This reluctance stems from the great variability of appearance of bone density by radiological examination, which depends largely on techniques for which there are as yet no reliable standards. Osteoporosis is suspected, however, when density is decreased and the appearance homogeneous, without the usual trabecular patterns being evident. The cortex appears thin, but may seem more dense by contrast with the remaining bone. In examining radiographs of osteoporotic vertebrae we have occasionally been impressed, as has Kesson,[2] by the absence of transverse trabeculae with preservation of vertical trabeculation. Pathological material shows that the horizontal trabeculae disappear before the vertical ones in senile osteoporosis.[3]

The structural changes accompanying osteoporosis of the spine are biconcavity of the vertebrae, which may be slight or of typical "codfish" form when biconcavity is extreme, and changes in the discs. The intervertebral discs may be expanded, but they are often narrowed. The difference probably depends on changes in elasticity of the nucleus pulposis and on the integrity of vertebral ligaments and muscles.

DIFFERENTIAL DIAGNOSIS

Osteoporosis of any etiology except that of disuse tends to have the above-mentioned characteristic radiographic distribution. A similar picture, however, may be seen in other conditions, notably osteomalacia and metastatic malignant disease.

The term osteomalacia should be reserved exclusively for the condition in which bone matrix is formed but remains uncalcified because of deficiency of calcium or an error in calcification processes. The calcium phosphorus product in the serum is low, and the serum alkaline phosphatase is elevated, since the weak bone in this instance appears to be capable of stimulating increased osteoblastic activity. The density of the entire skeleton tends to be decreased as seen roentgenographically, and pathognomonic pseudofractures may be evident. Dental lamina dura, preserved in osteoporosis, may be absent. Although back pain is common, it is usually accompanied by pain in the hips, hands, and feet, often with diffuse bony tenderness.

Metastatic malignant disease and multiple myeloma may present with only the characteristic symptom of osteoporosis: back pain. A careful history may suggest no other disturbances; radiographs may show only diffuse decrease in bone density, without localized or mottled areas of destruction or overgrowth of bone. Unless one considers osteoporosis to be a diagnosis by exclusion, such instances may be missed. Rarely, even after careful study, the diagnosis is missed until postmortem examination shows the vertebrae to be diffusely infiltrated with carcinoma or myeloma. Bachman [4] found that in 31 spines with metastases x-ray examination detected them in only 15 cases. In addition to serum calcium, phosphorus, and phosphatase values, and a quantitative urine calcium determination, a white blood cell count, hemoglobin determination, and serum albumin and globulin measurements should be made rou-

tinely in all cases in which the diagnosis of osteoporosis is entertained, with other studies as indicated. Although osteolytic lesions occasionally produce hypercalcemia, particularly if renal function is abnormal, and although occasionally the alkaline phosphatase is elevated in either osteolytic or osteoblastic metastatic disease, more often the serum values will be normal. With osteolytic lesions the urinary calcium is almost always increased.

Hyperparathyroidism may cause diffuse spinal rarefaction, but this probably never occurs in the absence of other bone symptoms and more characteristic lesions in the long bones and skull. In hyperparathyroidism the serum calcium is high, the serum phosphorus low, and the alkaline phosphatase elevated.

Hyperthyroidism, acromegaly, and Cushing's syndrome: The occasional difficulty in diagnosing hyperthyroidism in elderly persons is well known. It is just such hyperthyroidism which tends to be associated with bone disturbances, since, being inapparent, it may continue for a long period of time. There is still some uncertainty as to the nature of the bone lesion in thyrotoxicosis, whether it is osteitis fibrosa, osteomalacia, or osteoporosis.[5] It may be that all are present or that the diet determines which predominates. Results of serum chemistry studies tend to be normal, although the serum calcium may be slightly high and the alkaline phosphatase and urine calcium may be elevated. Acromegaly and Cushing's syndrome may present because of symptoms referable to the osteoporosis which is common in both, before the underlying condition is readily apparent. Serum values tend to be normal in Cushing's syndrome, with a frequently elevated urine calcium. In acromegaly the serum phosphorus is usually high, as is the urine calcium, while the serum calcium is normal.

Other causes of acute or chronic back pain may bring the elderly patient to the physician, the most common of which are osteoarthritis and the disorder known variously as "lumbago," "fibromyositis," "slipped disc," or "sciatica," all of which are possibly due to herniation of a nucleus pulposis.[6] Since some degree of osteoporosis and osteoarthritis may be expected in all elderly persons, and since a herniated nucleus pulposis and/or nerve compression may occur with osteoporotic fracture, it is often impossible to tell how much of the symptomatology is due to osteoporosis per se and how much to one or another of these other conditions.

TREATMENT OF SENILE OSTEOPOROSIS

Two related questions may properly be asked before discussing the recommended methods of treating senile osteoporosis: 1. Is there evidence that the condition is potentially reversible? 2. What are the criteria to be used in evaluating therapy?

Since the diagnosis is usually by history and radiological examination in conjunction with normal laboratory data excluding other conditions, definitive improvement would consist of a return toward normal of radiographic structural and density changes. No convincing evidence has been produced that such changes have resulted from any of the recommended forms of treatment of senile osteoporosis. Increased density that is seen on radiographs where improvement has been claimed appears to us to be due to hypertrophic changes accompanying healing of fractures, or to differences in technique.

With present radiological techniques and standards it is variously estimated that between 10% and 60% change in the calcium content of bone may occur before there is definite evidence of change by roentgenological examination. Considerable improvement, therefore, may occur before x-ray examination is capable of demonstrating it. Possibly better methods of comparing radiographs and of measuring small changes in bone density will reveal changes in the desired direction. Although trabeculae may theoretically increase in thickness under therapy, it is possible that those which have disappeared may be irreplaceable, since the surface on which new bone would form is missing. Return to full normal density would not then be expected.

The inelastic senile disc may be permanently incapable of recompression, and no structural reversal has been described in elderly persons treated for osteoporotic vertebral fracture.

If one looks for radiological evidence of reversibility in other forms of osteoporosis affecting the spine, the search is no more fruitful. Albright [7] has shown, in an interesting series of radiographs, that after cure of Cushing's syndrome in a growing child, the biconvex intervertebral discs were recompressed to almost normal size and shape by growth of new vertebral bone. As can be seen in these films, although the new bone is of normal density the bone which became osteoporotic when the disease was active remains so at the core of the new bone formation. Unfortunately, we have no data on the condition of the spine after osteoporosis from temporary immobilization. In temporarily immobilized long bones of growing children, osteoporosis is presumably reversible by growth and remodeling. We are less certain that the long bones of adults under similar circumstances return fully to normal, although they may appear so by x-ray examination.

Two other criteria may be used in estimating the efficacy of treatment: (1) demonstration that relief of symptoms is actually related to treatment and (2) balance studies of calcium.

The severity and duration of symptoms from the time they first appear in cases of senile osteoporosis is very variable. Symptoms may be acute and severe, lasting from a few days to many months, or they may be mild, chronic, or intermittent, also with longer or shorter duration. This variability applies equally to those with mild compression and those with severe fracture, the degree of disability often not agreeing with the degree of radiological involvement. Thus, a diagnosis of osteoporosis may be debatable by x-ray examination and yet symptoms may be severe. The reverse is also seen: films may show extensive osteoporosis in completely asymptomatic persons. Gershon-Cohen's studies [8] on residents of a home for the aged are relative to this point. One hundred thirty-six residents, ranging from 63 to 95 years of age, who were ambulatory and without complaint of back pain, were examined radiologically. Twenty-four (29%) of the women and 11 (20%) of the men were found to have osteoporosis with from one to seven compression fractures.

In no report of an allegedly specific form of treatment has the notation that symptoms were diminished or their duration shortened been more than an impression. In no report is there a statistically significant series of paired treated and untreated cases.

Balance studies are at present the one way by which we believe repair of osteoporotic bone can be demonstrated. As discussed above, when the skeleton is normal, the individual is in calcium balance; where there is progressive osteoporosis, calcium balance will be negative. It follows that if a negative balance can be brought to normal the process has been arrested and that if a positive balance is achieved it can be inferred that repair of bone is taking place. These conclusions are based on two postulates: (1) that more than 99% of the body calcium is contained in the skeleton and teeth and (2) that this calcium is structurally bound and that bone calcium increases only with an increase in bone matrix. Thus, for a positive balance of calcium to be present in persons with osteoporosis, matrix must be being formed in excess of bone resorption. The positive calcium balance is then an indicator of such matrix formation. As previously noted, the amount of nitrogen in the bone matrix inferred to have been formed, on the basis of positive calcium balance achieved, is too small to be demonstrated by the methods used in balance studies.

Repeated biopsies might conceivably be informative, but no extensive study by this means has yet been made. Studies with radioisotopes of calcium may provide a means of studying bone repair, but this probably must await a calcium isotope with a shorter half-life than those presently available.

Use of Sex Hormones in Treatment of Senile Osteoporosis

The initial impetus to the experimental use of estrogen in the treatment of osteoporosis came from observations in birds that estrogen led to marked calcium retention in newly formed endosteal bone, the retained calcium later being used in shell formation. In the human, estrogen appears to have a general effect on bone growth. There is still some question as to whether it acts independently as an anabolic agent or whether it acts to counteract the antianabolism of S-hormone and possibly the effect of growth hormone. That it can diminish the hypercalcuria induced by exogenous cortisone [9] suggests the latter action; that it not only can prevent negative calcium balance but can actually produce a positive calcium balance suggests the first action. Probably it acts in both ways. The result appears to be a stimulation of the osteoblasts.

In humans exogenous estrogen is probably effective on bone metabolism only when endogenous gonadal hormones are deficient or absent. There appears to be a ceiling beyond which an increase in dosage has no further effect.

In conjunction with the initial studies [10] it was observed that androgen could cause further increases in positive balances once the ceiling with estrogen had been achieved. This seems most definite when estrogen is given to an estrogen-deficient female, there being little evidence that androgen enhances the calcium balance in instances in which endogenous estrogen production is normal, and probably reflects N-hormone deficiency. Thus, in the postmenopausal woman estrogen can lead to significant increases in calcium retention, the ceiling of which can be exceeded by adding androgen to the regimen. It appears doubtful that either exogenous estrogen or androgen or the two combined have any significant effect on bone matrix formation, and hence on calcium balance, in the normal premenopausal female.

In the male with normal adult levels of androgens, neither estrogen nor androgen appears to have any marked effect on calcium balance. In the male with declining or absent androgens, both androgen and estrogen appear capable of causing a positive calcium balance. Some evidence suggests that the effect which can be obtained with estrogen is greater in the elderly woman and that that obtainable with androgen is higher in elderly men, but there are as yet few data on this point.

In addition to the effect of androgens on bone metabolism, their ability to cause marked nitrogen retention and muscle anabolism adds to their usefulness in the treatment of osteoporosis, since better musculature will support and protect the weakened bone against stress.

Balance studies performed in this hospital have been previously reported.[11] One, of three months' duration performed at intervals during a six-month course of estrogen therapy in a patient with postmenopausal osteoporosis, showed a sustained increase in calcium balance averaging 48 mg. per day when compared with a 25-day control period. In a man with senile osteoporosis treated with estrogens and androgens separately and in combination during 424 days of a 527-day period of observation, during which time balance studies were carried out for 290 days, the average increase in calcium retention over control values was for estrogen, 106 mg. per day; for androgen, 163 mg. per day, and for combined therapy, 225 mg. per day.* Other studies have shown similar, and in some instances greater, influences on calcium balance over long periods of time. Similar results have been reported by other investigators.†

If one assumes that radiologically evident osteoporosis is the result of 30% loss of body calcium, it can be calculated that with a positive balance of 100 mg. per day it would

* Cases 3 and 6. Calculations of average balance have been made using only those periods not influenced by preceding treatment, e. g., after-control periods are not included in control averages, since estrogen effect may persist up to 30 days after withdrawal. For the same reason, periods in which testosterone immediately followed estrin are not included in the calculations of testosterone effect.

† References 12-14.

take more than nine years for full reossification to occur. This consideration, with the previous remarks on potential reversibility of osteoporosis, makes it less surprising that no definite evidence of repair has been obtained by roengenograms. That films of hormone-treated patients fail to show advance of osteoporosis is, however, encouraging. We share with others the impression that estrogen treatment diminishes the severity and duration of symptoms, but until detailed statistical surveys are made this remains an impression.

There has been some trepidation about the use of sex hormones in elderly persons, which we do not believe is valid if certain precautions are taken. The major objections to the use of estrogen have been, in the female, possible carcinogenesis, fluid retention, changes in libido, and vaginal bleeding. In the male the first three of these objections have been raised, plus those of gynecomastia and testicular damage. Cosmetic considerations have been the primary objection to the use of androgen in the famale, and testicular damage, to its use in men. In both sexes carcinogenesis, fluid retention, and effects on libido have been considered to be problems in the use of testosterone.

A carcinogenic effect of sex hormones has been amply demonstrated in animals, but it remains unproved that there is such in humans, although their ability to maintain and to accelerate cancer is well known. Despite an extensive use of such hormones over many years, I do not believe that the incidence of genital or breast carcinoma is greater in the treated patients than for the general population. Nonetheless, it is desirable in the female patient to perform vaginal smears every 6 to 12 months and to make similarly spaced breast and pelvic examinations. In hormone-treated males, prostatic examinations should be made regularly.

There is no doubt that fluid retention may be caused by estrogen. In the doses used in this clinic, however, fluid retention, if it occurs, is mild and of short duration. It can be guarded against, in the patient with known or suspected cardiorenal disease, by the use of salt restriction in the early phase of treatment. Rarely has digitalization or the use of diuretics been necessary because of estrogen treatment in cases where they were not already previously indicated. Testosterone almost never causes fluid retention which is clinically significant.

Undesirable enhancement of libido is almost never a difficult problem in women treated with estrogen; in men diminution of libido on this medication may present difficulties. In both men and women testosterone may increase libido, but this is only occasionally a problem. The use of combined estrogen and androgen therapy usually minimizes undesirable effects.

We do not consider vaginal bleeding to be something to be avoided during treatment of older women with estrogen. In fact, therapy is designed to produce regular estrin-withdrawal flowing. The patient is urged to keep a record of medication and of bleeding. If bleeding occurs at unexpected times, i. e., at times other than after estrogen has been withdrawn, appropriate investigations are made to rule out the possibility of carcinoma.

Prolonged use of estrogen in the male may be complicated by gynecomastia, by reduction of libido, and by temporary or permanent sterility. Testosterone will suppress spermatogenesis, and this change may be permanent. Sterility is rarely a problem for the aged man; gynecomastia and reduced libido may present real difficulties. The rate and degree to which a given dosage will produce such effects is very variable from person to person. Combining testosterone with estrogen will tend to reduce the rate and degree to which gynecomastia and diminished libido occur.

Similarly, the rate and degree to which androgen produces frontal balding, facial hirsutism, and deepening of the voice in women varies from patient to patient. Combined therapy tends to slow the appearance of these undesirable cosmetic effects.

In practice, our main standby of treatment in women with senile osteoporosis is diethylstilbestrol (Stilbestrol), in a dose of 1 to 5 mg. daily to be taken for four weeks, then omitted for 7 to 10 days, in repeated courses

for an indefinite period of time. Four weeks of treatment usually permits sufficient building up of endometrium for menstruation to occur during the time when estrogen is not given. Diethylstilbestrol is the estrogen of choice because of its low cost and because it can be taken by mouth. When it leads to nausea which is persistent and not relieved by having the patient take the medication at bedtime, conjugated estrogenic substances (Premarin), in doses of 1.25 or 2.50 mg. per day on a similar regimen, is prescribed. Ethinyl estradiol, in doses of 0.1 to 0.2 mg., is an occasional third choice if there are untoward effects from conjugated estrogenic substances. Only very rarely is a patient unable to tolerate an oral preparation. In such instances, and where oral medication is otherwise contraindicated, estradiol dipropionate, 5 mg. intramuscularly, is given each week for four weeks and then omitted for one week. In an occasional patient these regimens do not produce regular withdrawal bleeding, for reasons which are not understood. In the patient who complains of severe hot flashes during the time off medication, continuous estrin therapy may be given, with a five-day course of progestational hormone (pregneninolone, 10 mg. orally five times daily for five days, or progesterone, 5 mg. intramuscularly each day for five days) every five weeks. Vaginal bleeding usually follows the last dose within 48 hours.

Treatment is usually begun with estrogens, as described above, and with androgen, usually a 5 or 10 mg. methyltestosterone Linguet every day or every other day. The estrogen is continued indefinitely. Testosterone is usually given only for four to eight weeks, or until one or another sign of masculinization first appears. An occasional patient will tolerate small doses of testosterone indefinitely without evidence of masculinization. If osteoporosis and general debility are severe, it may be desirable to continue testosterone indefinitely despite side-effects.

In the male with senile osteoporosis, estrogen, in the doses given above, together with testosterone, is used to initiate treatment. With the appearance of undesirable side-effects the estrogen is discontinued and testosterone continued. When osteoporosis is severe, estrogen may be continued beyond the point of femininization. Since senile osteoporosis is often progressive, testosterone should probably be continued indefinitely, despite the possible damage of long-term therapy to the testes. Although we favor buccal medication in the amount of 20 to 30 mg. daily by Linguets of methyltestosterone, it is sometimes more desirable to give injections of 50 mg. of testosterone propionate two or three times weekly. Long-acting testosterone esters (testosterone cyclopentylpropionate, testosterone enanthate, etc.) are now available which can be given once every two to four weeks in the amount of 100 to 250 mg.

Diet and Dietary Supplements

1. *Protein.*—Because osteoporosis has been defined as a deficiency of bone matrix, because the matrix is a protein, and because protein deficiency can produce osteoporosis, the use of a high-protein diet has frequently been advocated, and we usually follow this procedure. It should be repeated, however, that many patients with senile osteoporosis have adequate protein intakes and are without demonstrable protein deficiency and that the difficulty is one of disturbed utilization rather than of insufficient intake. If there were dietary protein deficiency one would expect to find a positive nitrogen balance instead of the frequently observed continued negative balance despite high-protein intakes. When protein-deficient dietary histories are obtained, high-protein diets are definitely indicated and protein supplements are in order.

2. *Calcium.*—There is still no general agreement as to the calcium requirement of normal young adults, although many studies have shown the requirement to be between 8 and 12 mg./kg./day (560 to 840 mg./70 kg./day).‡ There is less agreement among

‡References 15 and 16.

studies in old adults, in whom some investigators find the requirement to be no different from that in young adults, while others find a requirement of up to 1500 mg. daily.

Bogdonoff [17] studied seven elderly osteoporotic men on diets in which the calcium was progressively varied from 107 to 1600 mg. per day and concludes that approximately 850 mg. of calcium per day is required to effect calcium equilibrium in old adults and that when larger amounts of calcium are supplied retention of calcium is not strikingly increased. Robert,[18] in nine elderly women, and Ackerman,[19] in eight elderly men, calculate the requirement to be 14.1 and 18.5 mg./kg./day, respectively (987 and 1295 mg./70 kg./day). Shorr [20] agrees that there is a ceiling above which increased dietary calcium does not lead to increased retention, but he places this level between 1500 and 2000 mg. daily. Anderson [12] concludes that a calcium intake of "about twice the normal levels must be given" to insure the maximum effect on calcium retention of estrogen.

I have not felt that calcium intakes above 800 mg. daily enhance calcium retention in patients with senile osteoporosis. This is the approximate amount of calcium in the normal diet in which no milk-by-the-glassful is included. In the patient who through anorexia or dietary peculiarity has a distinctly low calcium intake, two glasses of milk will provide 550 mg. of calcium. If such patients refuse to drink milk, calcium lactate tablets in the amount of 5 gm. daily will provide 650 mg. of calcium. The aid of an experienced dietician can profitably be utilized in assessing the calcium and protein intake and in finding ways of normalizing these.

Our objection to the use of high-calcium diets in old persons with osteoporosis is that the unutilizable calcium may increase an already high urinary calcium and favor the formation of kidney stones. If, in addition to osteoporosis, there is also a suggestion of osteomalacia, then increased calcium and vitamin D are of course indicated. In this connection it should be remembered that following an acute osteoporotic fracture the alkaline phosphatase may be moderately elevated, and it will be high in Paget's disease, which is frequently inapparent. In true osteomalacia the calcium × phosphorus product will be low; in Paget's disease, both calcium and phosphorus are normal.

3. *Vitamin D.*—The above discussion on calcium applies also to vitamin D, the use of which has been recommended to enhance calcium absorption in patients with osteoporosis. Since osteoporosis is a disorder of matrix formation and not one of calcium deficiency, extra absorption of calcium in the absence of osteomalacia and in the absence of newly formed bone matrix will only increase excretion of calcium in the urine, with the added hazard of stone formation. We would suggest that Vitamin D not be used in the treatment of osteoporosis.

4. *Vitamin B_{12}.*—Vitamin B_{12} has recently been mentioned in a preliminary report as having produced marked symptomatic relief in two patients with osteoporosis,[21] and it has subsequently been advertised for this purpose. There is no evidence to date of vitamin B_{12} deficiency in patients with senile osteoporosis nor in older persons in general.

5. *Vitamin C.*—Except in those rare instances in which true scurvy exists, there is no evidence that vitamin C deficiency plays any role in senile osteoporosis. When there has been a poor diet, vitamin C as well as B vitamins should be administered. The routine use of vitamin C in senile osteoporosis would be supported by observations that serum levels in old persons tend to be lower than those of young adults.[22]

Strontium

Strontium, a divalent metallic element which, like calcium, is retained in the body almost entirely in bone, presumably as a triphosphate salt in an apatite crystal lattice, has been advocated in the treatment of osteoporosis by Shorr and Carter.§ These investi-

§ References 13, 20, and 23-25.

gators believe that, when maximum retention of calcium has been obtained, strontium is independently well absorbed and may be retained in significant amounts for prolonged periods of time without untoward effect.

The balance studies as reported are difficult to evaluate. In some instances calcium intake was modified during the periods when strontium was administered; in others, although calcium intake remained constant, results are obscured by the addition of vitamin D, estrogen, or androgen close to the time when strontium was added. In several studies there appears to be a decrease in calcium retention when strontium is added and the combined calcium plus strontium retention in millimols (the atomic weight of calcium is 40.07; that of strontium is 87.63) is no greater than that of calcium alone in the control periods. This would be the expected situation if strontium were merely replacing calcium in the bone matrix. In other studies the combined retention does appear to be greater than that of calcium alone. That this may be due to the ability of strontium to be deposited when enzyme systems for depositing calcium are saturated, we cannot agree, since there is no evidence of any calcification error in osteoporosis. That strontium induces increased matrix production seems unlikely, leaving the possibility that strontium is deposited in a form different than that of calcium and that matrix can hold more strontium than calcium. Evidence that strontium actually increases bone tensile strength is awaited with interest.

Shorr concludes that

> although this is a point difficult to quantitate, the clinical improvement in the osteoporotic patients receiving strontium appears to proceed at a rate which corresponds to the greater total storage of "lime salts" that is achieved by the combined administration of both strontium and calcium.

We have had no experience in the use of strontium in the treatment of senile osteoporosis. Our only reservation to its use is that the urinary excretion of strontium may conceivably lead to the formation of strontium phosphate stones.

Orthopedic and Other Procedures

Since stresses and strains are the major stimuli to bone formation, an aim of all treatment should be to permit continued activity so that disuse atrophy will not further reduce the already insufficient bone production. Pain is almost the only deterrent to activity, since rarely does a fracture result in sufficient impingement on nerves to result in paralysis. The pain of an acute fracture may be of short duration, but it is often quite prolonged. All too often orthopedic procedures aimed at reducing pain result in enhancing osteoporosis, leading to further fractures of vertebrae and long bones when activity is resumed. It has been the policy of the orthopedic service of this hospital to minimize immobilization while trying to achieve stability of the spine and relief of pain. For this reason plaster immobilization is almost never used, and braces when worn are kept to a minimum both as to their physical size and the length of time during which they are worn. Braces need not be worn at all times, and more often it is suggested that they be used only during the period of the day when the patient is most active. If osteoporosis is not severe, and if mobilization can be effected without a brace, none is prescribed. A well-fitted corset is often preferable and may provide better and more comfortable support. If osteoporosis is severe and pain acute, a brace may be ordered soon after the diagnosis is made, analgesia as indicated is prescribed, and rapid mobilization is effected. Unfortunately, the severity of the pain may occasionally not permit this for many weeks. In such instances a peripheral nerve block may interrupt pain reflexes and permit mobilization. Acetylsalicylic acid however, is the main standby of pain relief once the initial acute pain has subsided.

It should be axiomatic that the known osteoporotic patient undergoing surgery or during any illness should be immobilized as little as possible. This applies equally to old persons without known or symptomatic osteoporosis, since a number of patients presenting with osteoporosis give a history of prior prolonged illness and bed rest.

When immobilization is necessary, the use of a vibrating mattress or oscillating bed may prove effective in providing stresses and strains to prevent further diminution of osteoblastic activity. Unfortunately, little evidence has yet been obtained to show that these mechanical devices are effective in this group of patients, although the bed has been found to be so in decreasing calcium loss in immobilized normal persons.[26] During extensive immobilization it is well to limit calcum intake, because urinary calcium will be high under such circumstances and additional dietary calcium with urine stasis will favor stone formation. A regular high-protein diet should be given, with no milk-by-the-glassful, and with no cheese. In the aged person bone resorpton is rarely great enough for cessation of osteoblastic activity by immobilization to result in hypercalcemia, but this is a possible danger, particularly if renal function is impaired or if Paget's disease is present.

Physical therapy, with postural and muscle-strengthening exercises within the limits of pain, is an important part of the program of the osteoporotic patient.

SUMMARY

Senile osteoporosis is a physiological condition in which bone production is less than bone resorption. It appears to be due to deficient osteoblast stimulation.

Calcium metabolism and serum levels of calcium, phosphorus, and alkaline phosphatase are normal; urine calcium tends to be increased and is an index of the degree of activity of the process.

One of the main etiological factors is considered to be a relative preponderance of antianabolic over anabolic hormones.

The efficacy of therapy can theoretically be assessed by radiological changes, symptomatic improvement, repeated biopsies, studies with radioisotopes of calcium, or by calcium balance studies. Only the last has been proved to be a useful index at the present time.

Therapy should consist of analgesia and rapid mobilization in instances in which there has been acute symptomatic fracture. Continued mobility and muscle-strengthening exercises should be obtained in all cases. Long-term maintenance is recommended on a high-protein diet with up to 1000 mg. of calcium per day, with B vitamins and ascorbic acid if desired, but without vitamin D. Women are maintained on estrogen, with testosterone being used initially and up to the point of masculinization; men are maintained on androgen, with estrogen given initially and until femininization becomes disturbing. Continued combined androgen and estrogen therapy may be desirable in both men and women when osteoporosis is severe and general debility is present.

Prolonged immobilization is to be avoided in patients with osteoporosis and in elderly patients in general.

REFERENCES

1. Albright, F.: Osteoporosis, Ann. Int. Med. **27**:861, 1947.

2. Kesson, C. M.; Morris, N., and McCutcheon, A.: Generalized Osteoporosis in Old Age, Ann. Rheumat. Dis. **6**:146, 1947.

3. Panella-Casas, M., and Monteys-Orta: La Cyphose sénile ostéoporotique, Rev. méd. Liege **5**: 697, 1950.

4. Bachman, A. L., and Sproul, E. E.: Correlation of Radiographic and Autopsy Findings in Suspected Metastases in the Spine, Bull. New York Acad. Med. **31**:146, 1955.

5. Follis, R. H.: Skeletal Changes Associated with Hyperthryroidism, Bull. Johns Hopkins Hosp. **92**:405, 1953.

6. Charnley, M. B.: Acute Lumbago and Sciatica, Brit. M. J. **1**:344, 1955.

7. Albright, F.: The Effect of Hormones on Osteogenesis in Man, Recent Progr. Hormone Res. **1**:293, 1947.

8. Gershon-Cohen, J.; Rechtman, A. M., Schraer, H., and Blumberg, N.: Asymptomatic Fractures in Osteoporotic Spines of the Aged, J. A. M. A. **153**:625, 1953.

9. Henneman, P. H.; Irwin, J. W.; Wang, D. M. K., and Burrage, W. S.: The Effect of Estrogen and Androgen on Calcium Metabolism During Cortisone Administration, J. Clin. Endocrinol. **15**:858, 1955.

10. Albright, F.; Bloomberg, E., and Smith, P. H.: Post-Menopausal Osteoporosis, Tr. A. Am. Physicians **55**:298, 1940.

11. Reifenstein, E. C., and Albright, F.: The Metabolic Effects of Steroid Hormones in Osteoporosis, J. Clin. Invest. **26**:24, 1947.

12. Anderson, I. A.: Post-Menopausal Osteoporosis: Clinical Manifestations and Treatment with Oestrogens, Quart. J. Med. **19**:67, 1950.

13. Shorr, E., and Carter, A. C.: The Value of Strontium as an Adjuvant to Calcium in the Remineralization of the Skeleton in Osteoporosis in Man, in Reifenstein, E. C. Jr., and Johnson, V. Editors: Metabolic Interrelations: Transactions of the Second Conference, New York, Josiah Macy, Jr., Foundation, 1950, p. 144.

14. Bogdonoff, M. C.; Shock, N. W., and Parsons, J.: The Effect of Stilbestrol on the Retention of Nitrogen, Calcium, Phosphorus, and Potassium in Aged Males with and without Osteoporosis, J. Gerontol. **9**:262, 1954.

15. Outhouse, J.; Breiter, H.; Rutherford, E.; Dwight, J.; Mills, R., and Armstrong, W.: The Calcium Requirement of Man: Balance Studies on Seven Adults, J. Nutrition **21**:565, 1941.

16. Steggerda, F. R., and Mitchell, H. H.: Variability in the Calcium Metabolism and Calcium Requirements of Adult Human Subjects, J. Nutrition **31**:407, 1946.

17. Bogdonoff, M. C.; Shock, N. W., and Nichols, M. P.: Calcium, Phosphorus, Nitrogen and Potassium Balance Studies in Aged Males, J. Gerontol. **8**:272, 1953.

18. Robert, P. H.; Kerr, C. H., and Ohlson, M. A.: Nutritional Status of Older Women: Nitrogen, Calcium, and Phosphorus Retention of 9 Women, J. Am. Dietet. A. **24**:292, 1948.

19. Ackerman, P. G., and Toro, G.: Calcium and Phosphorus Balance in Elderly Men, J. Gerontol. **8**:289, 1953.

20. Shorr, E., and Carter, A. C.: The Usefulness of Strontium as an Adjuvant to Calcium in the Remineralization of the Skeleton in Man, Bull. Hosp. Joint Dis. **13**:59, 1952.

21. Hallahan, J. D.: Symptomatic Relief of Osteo-Arthritis and Osteoporosis with Vitamin B_{12}: A Preliminary Report, Am. Pract. & Dig. Treat. **3**:27, 1952.

22. Kirk, J. E., and Chieffi, M.: Vitamin Studies in Middle-Aged and Old Individuals: XI. The Concentration of Total Ascorbic Acid in Whole Blood, J. Gerontol. **8**:301, 1953.

23. Shorr, E.: Effect of Strontium on the Calcium Balance of Patients with Osteoporosis, in Metabolic Aspects of Convalescence: Transactions of the Sixth Meeting, New York, Josiah Macy, Jr., Foundation, 1944, p. 125.

24. Shorr, E., and Carter, A. C.: Studies on the Effects of Estrogens, Androgens and Vitamin D_2 on Calcium and Strontium Metabolism, in Reifenstein, E. C., Jr., and Johnson, V., Editors: Conference on Metabolic Aspects of Convalescence: Transcactions of the Fifteenth Meeting, New York, Josiah Macy, Jr., Foundation, 1946, p. 99.

25. Shorr, E., and Carter, A. C.: Strontium as an Adjuvant to Calcium in the Treatment of Post-Menopausal Osteoporosis, in Conference on Metabolic Aspects of Convalescence: Transactions of the Sixteenth Meeting, New York, Josiah Macy, Jr., Foundation, 1947, p. 122.

26. Whedon, G. D.; Deitrick, S. E., and Shorr, E.: Modification of Effects of Immobilization upon Metabolic and Physiologic Functions of Normal Men by Use of an Oscillating Bed, Am. J. Med. **6**:684, 1949.

Progress in Internal Medicine

DIABETES INSIPIDUS

Clinical and Experimental Studies with Consideration of Genetic Relationships

J. FLOYD CANNON, M.D., Salt Lake City

DIABETES insipidus was first differentiated from diabetes mellitus by Thomas Willis, in 1674. The term diabetes is derived from the Greek word for syphon, and insipidus differentiates this disease from mellitus, which connotes a honey taste. Diabetes insipidus has been defined as a chronic affection marked by extreme thirst, polyuria, nocturia, and an absence of glycosuria. In this study those affected with hereditary diabetes insipidus are referred to among their families by terms such as "water topers," "drinkers," "drinking babies." It is a relatively rare condition seen in all ages and both sexes; however, it is noted more frequently in males than in females. The basis for this finding is demonstrated in the following study.

CLASSIFICATION

Clinically and etiologically diabetes insipidus is divided according to the following classification, the basis for which is presented in this study:

1. Pituitary type: There is pituitary deficiency, in which the symptoms are relieved by the administration of pituitary products
   (*a*) Primary (hereditary)
   (*b*) Secondary (postinfectious, neoplasms, etc.)
2. Extrapituitary type: The administration of pituitary products does not relieve the symptoms; this type may be renal, with inadequate reabsorption, or it may be hypothalamic
   (*a*) Primary (hereditary)
   (*b*) Secondary (postinfectious, etc.)
3. Psychogenic polydipsia.

HEREDITARY FACTOR (HISTORICAL)

The factor of heredity in diabetes insipidus has been of particular interest since it was first described by Lacombe,* in 1841. All investigators of the subject have emphasized the importance of the hereditary factor, and several have published their findings (Table 1).

The following is a brief summary bringing up to date the histories of the families studied with the clinically significant findings of each group noted.

Lacombe † (1841): Eight cases (five males and three females); two generations studied. Some of his patients were affected from earliest infancy; some died at a very advanced age. One patient drank water on an average of a liter an hour.

Deebrey ‡ (1859): Five cases (two males and three females); two generations. One

Submitted for publication March 30, 1955.

* Cited by de Lange.[1]

† Cited by de Lange [1] and Bullock.[3f]

‡ Cited by de Lange [1] and Bullock.[3h]

of his patients passed 25 liters in 24 hours. This patient had the onset of the disease at 2 years of age.

Wachsmuth § (1863): Two cases (both males); one generation. One patient suffered from the disease from infancy. The physician locked himself in a room with the patient for days, and after observation of the patient and his habits concluded that thirst was the primary factor.

present study. As also mentioned in the present study, Gee noted that the newborn cried many hours after birth and could only be comforted by a drink of water. Three children died early in this group, one at 4 months. Two boys had the disease from 6 months of age.

Pain [3d] (1879): Seven cases (five males and two females); three generations. Tuberculosis was common in the family. One pa-

TABLE 1.—*Publications Discussing Heredity in Diabetes Insipidus* *

Year	Observer	Patients, No.			Generations, No.
		Total	Male	Female	
1841	Lacombe	8	5	3	2
1859	Deebrey	5	2	3	2
1863	Wachsmuth	2	2	..	1
1866	Reith	2	1	1	1
1875	Van der Heijden	10	..	..	..
1877	Gee	11	9	2	4
1879	Pain	7	5	2	3
1881	Orsi	6	5	1	2
1884	A. Weil, Sr.	35	19	14	6
1889	Clay	3	2	1	2
1892	McIraith	9	6	3	3
1893	Lauritzen	8	5	3	4
1893	Sasse	8	4	1	3
1895	Marinesco	6	6	..	2
1905	Knoepfelmacher	5	3	2	4
1908	A. Weil, Jr.	See A. Weil, Sr.			
1911	Ehrmann	3	3	..	1
1920	Maranon and Bonella	2	..	..	2
1921	Jansen and Broekman	14	4	10	5
1922	Martinez and Navarron	2	..	..	..
1924	Gaensslen and Fritz	19	10	9	5
1927	Chase	22	..	..	5
1933	Chester and Speigel	7	3	4	4
1934	deLange	8	2	6	4
1936	Levit and Pessikova	3 of family origin in 16 cases studied			
1942	Blotner	3	1	2	3
1946	Williams and Henry	7	7	..	5

* Lancereaux, 1869, had no cases of his own but summarized the work of Lacombe, Wachsmuth, Deebrey, and Reith.

Reith [3j] (1866): Two cases (one male and one female); one generation. One patient had suffered with the disease from earliest infancy.

Van der Heijden (1875): Ten cases.

Gee [3n] (1877): Eleven cases (nine males and two females); four generations. One patient drank 1 gallon of water during each night. In one patient the symptoms abated with age. In this group two daughters carried the disease but did not have it themselves, which is significant in view of the

§ Cited by de Lange [1] and Bullock.[3k]

tient was affected with diabetes insipidus from infancy. One had a decrease in symptoms with advancing years. One drank easily several liters of wine and died after an excessive drinking bout.

Orsi [3e] (1881): Six cases (five males and one female); two generations. The mother of this family noted polyuria and polydipsia to a considerable degree only while pregnant. The children inherited the disease.

Clay [3g] (1889): Three cases (two males and one female); two generations. Tuberculosis was common in this family. All three of the patients developed diabetes insipidus

at 9 years of age. Increase in weight was coincident with increased secretion of urine.

McIlraith [31] (1892): Nine cases (six males and three females); four generations. Three boys were mentally retarded.

Lauritzen [3c] (1893): Eight cases (five males and three females); four generations. One patient drank 18,860 cc. per day. One boy had enuresis up to 20 years of age. (This symptom has also been noted in the present study.) The original patient in this study had symptom-free parents; thus there was probably an asymptomatic female carrier. One symptomatic female studied had no symptoms when pregnant; one had symptoms from birth.

Sasse [3m] (1893): Eight cases (four males and four females); three generations. Whether these were true cases is doubted by some. They drank about 3 liters daily, and the urine had a specific gravity of 1.020. By our present tests this would not be classified as diabetes insipidus.[15]

Marinesco ‖ (1895): Six cases (all males); two generations. A study was made of three males only. Both parents were healthy, but the mother noted excessive thirst during the childbearing period. One child studied had tuberculosis.

Knopfelmacher [31] (1905): Five cases (three males and two females); four generations. One of those affected had ichthyosis congenita.

Ehrmann ¶ (1911): Three cases (males); one generation. Three brothers were affected, and two sisters were normal.

Maranon and Bonella (1920): Twenty-five cases. Those classified as the primary type of diabetes insipidus were studied in two generations.

Jansen and Brockman (1921): Fourteen cases (4 males and 10 females); five generations. One patient in this group had tuberculosis.

Martinez and Navarron (1922): Two cases.

Gaensselen and Firtz # (1924): Nineteen cases (ten males and nine females); five generations. A dominant characteristic followed through five generations.

Chase [4] (1927): Twenty-two cases; five generations. In one generation 10 of 23 children were affected. The family knew of no complications of the disease. The father often drank a gallon of water at a time. He died at 85 years. In this family it was concluded that the disease was a dominant, non-sex-linked characteristic.

Chester and Spiegel [5] (1933): Seven cases (three males and four females); four generations. One patient had twofold urinary output during pregnancy. In two patients symptoms first appeared at 5 years.

de Lange [1] (1934): Eight cases (two males and six females); four generations. In this study an asymptomatic female had a symptomatic child. It was also noted that some of the patients had severer symptoms than others. Posterior pituitary, U.S.P. (Pituitrin) had no influence in one of these cases.

Levit and Pessikova (1936): Six cases, three of familial origin.

Blotner [13] (1942): One case. The mother and grandmother also had symptoms. The patient responded well to posterior pituitary.

Weil and Weil * (1884; 1908): Thirty-five cases (19 males and 14 females, 2 unknown but thought to be females); six generations, 220 in the family tree. This is the classic example of hereditary diabetes insipidus which has served as the basis for conclusions concerning the hereditary factor since it was first reported by Adolph Weil, in 1884, and carried further by his son Alfred Weil, in 1908. Just,† de Lange,[1] Chester and Spiegel,[5] Bullock,[3] and many others point out that it is an example of a simple dominant hereditary characteristic. de Lange [1] points out, however, that in two cases symptomatic children were born of asymptomatic mothers. (This type of hereditary factor is substantiated by the present study.) Weil stated that the general constitution of the

‖ Cited by de Lange.[1]

¶ Cited by de Lange.[1]

Cited by de Lange.[1]

* Cited by de Lange,[1] Bullock,[3a,b] and Chester and Spiegel.[5]

† Cited by de Lange.[1]

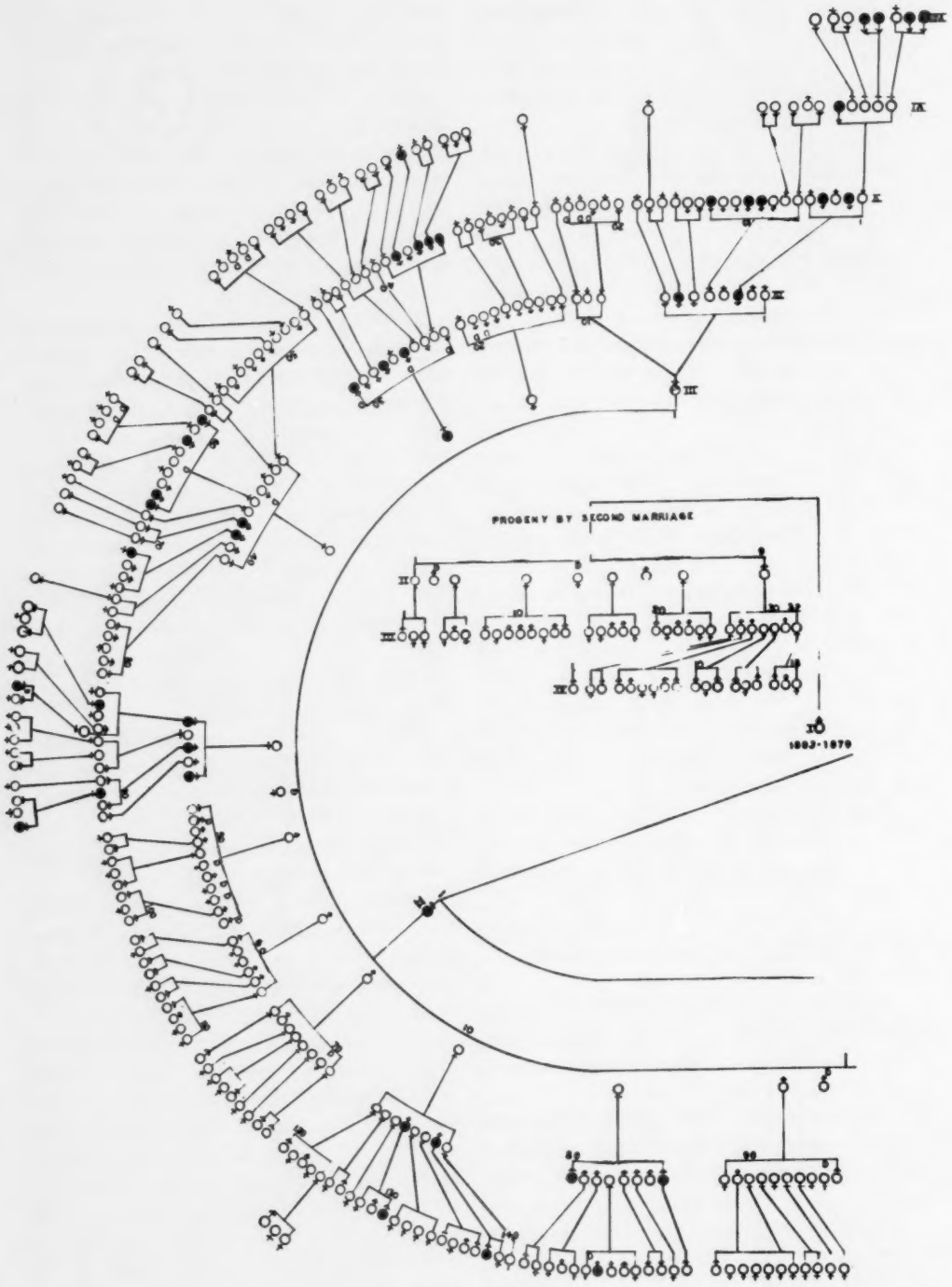


Fig. 1.—Family 1.

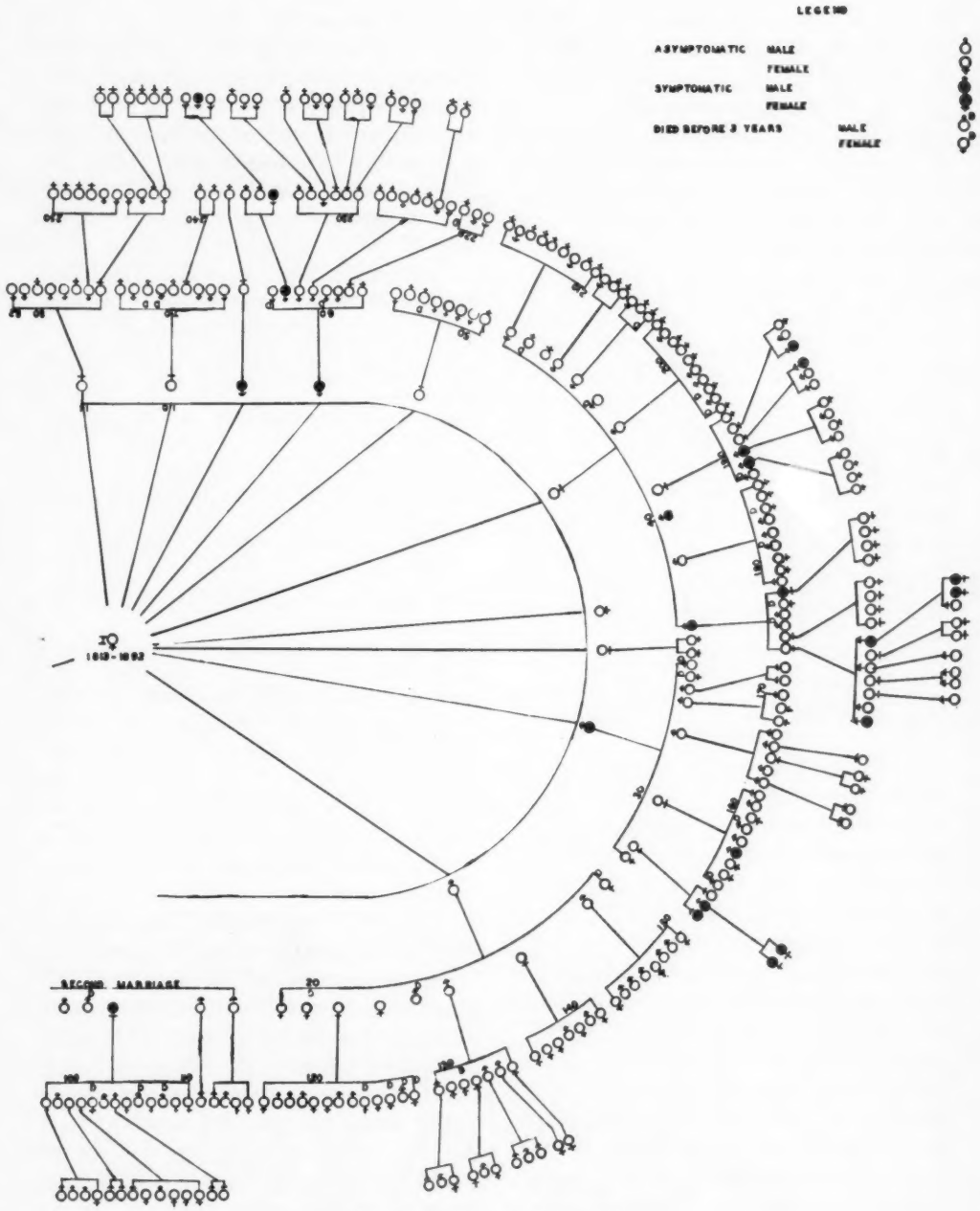


Fig. 1.—Family 1 (continued).

family was excellent. Two idiots were noted, but no insanity. Only a trace of a desire for alcoholic liquor was noted. Most of the deaths of the family were either at a very old age or in the first years of life. (The frequency of early deaths is also noted in the present study.)

Williams and Henry [28] (1947): Seven cases (all males); five generations. In this study the trait was transmitted by females only and appeared to be sex-linked. However, the number involved was too small to allow definite conclusions.

In most of the preceding cases the hereditary factor (being a simple, dominant, non-sex-linked characteristic) was maintained. However, in several cases the mothers were found to be asymptomatic (de Lange, Gee, Orsi, Clay, Lauritzen, and Marinesco, and de Lange as noted in Weil's study.) Weil's group was used as the basis of the hereditary study because it was well studied and large in number. The present study also involves enough cases to serve as a basis for conclusions to be drawn concerning the hereditary factor.

HEREDITARY FACTORS (PRESENT STUDY)

1. Extrapituitary Type, Primary (Hereditary)

In Family 1 (Fig. 1) the genealogical records were complete, thus facilitating the investigation. This family, except in the case of the family of Generation III, No. 16, and where later indicated, cooperated fully and made this study possible. The names and ages of all persons indicated in Family 1 are exact and known. The conclusions drawn as to persons with the characteristic are based upon the history, and upon laboratory tests where possible. It is shown later that the asymptomatic female carrier is normal as far as history and tests are concerned (see summary of blood and urinary findings). This increases the difficulty of following the hereditary factor, and it is for this reason that the males are used as a basis for determining the hereditary factor. The history of each positive case was checked before being included. The history obtained from the family is considered sufficient to classify the positive cases.

Family 1 (Fig. 1) shows that the original male had progeny by two marriages. The progeny by the second marriage has been completely symptom-free, thus proving that the original male (1803-1879) did not carry the hereditary factor. In this family a total of 59 persons have been studied. There are 28 males and 31 females, of whom 2 died before the age of 3 years. This small number of early deaths is considerably less than was found in the progeny by the first marriage. The progeny by the first marriage totals 679 persons. There are 350 males, 328 females and 1 "premature baby," the sex of which is unknown. The mother of this group (1813-1892) was asymptomatic according to the patient (Gen. III, No. 75) who lived and slept with her as a child. The progeny of this first marriage includes 55 symptomatic males, 11 symptomatic females, and 21 asymptomatic female carriers. It is very likely that there are many more who have not or will not have children, thus making

Table 2.—*Summary of Family 1*

	Generation							
	I	II	III	IV	V	VI	VII	Total
Progeny from 1st marriage *								
Symptomatic								
Male	..	4	3	20	21	3	4	55
Female	..	..	2	1	5	3	..	11
Total	..	4	5	21	26	6	4	66
Asymptomatic								
Male	..	..	..	..	..	..	..	..
Female	1	1	8	8	2	2	..	22
Total	1	1	8	8	2	2	..	22
Total involved	1	5	13	29	28	8	4	88
Family total								
Male	..	5	46	120	132	41	6	350
Female	1	6	36	130	118	35	2	328
Total	1	11	82	250	251	76	8	679
Progeny from 2d marriage								
Male	..	..	8	16	1	1	..	26
Female	..	..	7	16	4	4	..	31
Sex unknown	..	..	..	1	1	..	..	2
Total	..	..	15	33	6	5	..	59

* 8.5% died before 3 years of age.

it impossible to determine whether they carry the hereditary factor. A careful study has been made of the asymptomatic female carriers (Gen. IV, Nos. 83, 191, and 192, and Gen. III, No. 41; see summary of blood and urine findings). A very impressive example of how the characteristic may go unmarked through generations and later reveal itself is seen in this study. In the case of the patients in Gen. V, Nos. 223 and 224, the symptoms appear after four preceding generations of asymptomatic female carriers (Gen. I, No. 1; Gen. II, No. 6; Gen. III, No. 41; Gen. IV, Nos. 191 and 192, Family 1). Five of these have been studied in detail.

No asymptomatic male carrier of the hereditary factor was found. A study of the same group we find 6 symptomatic and 11 asymptomatic females, which indicates that the female may or may not show the symptoms of diabetes insipidus and still carry the factor.

It must be remembered that only those proved to have the symptoms or to carry the trait are considered positive and that all others are considered negative. In a large family where the hereditary trait is so marked the members are reluctant to give information and have been known to withhold it. Therefore, all the "negative" members are not necessarily negative. When one considers the progeny of the female carriers of the whole family (22 in number), it is noted they produced 40 positive males and

TABLE 3.—*Totals of Generations I and II and the Progeny of Generation II, No. 1*

Generation	Symptomatic			Asymptomatic			Total Involved	Family Total		
	Male	Female	Total	Male	Female	Total		Male	Female	Total
I	..	..	..	..	1	1	1	..	1	1
II	3	..	3	..	1	1	4	5	6	11
III	..	2	2	..	5	5	7	10	8	18
IV	14	..	14	..	4	4	18	29	23	52
V	14	3	17	..	..	..	17	32	20	52
VI	1	1	2	..	..	..	2	6	5	11
Total	32	6	38	..	11	11	49	82	63	145

males of Generations I and II and the male progeny of Generation II, No. 1, reveals some interesting findings concerning the hereditary factor. This was the first group thoroughly studied. Table 3 gives the totals of the families in which the trait has been found. It is noted that in Generation II there are three males with the hereditary trait. Five males are found in this generation. In Generation III there are 10 males, none of whom has the trait, but in this generation 7 persons of a total of 18 are involved and they consist of symptomatic and asymptomatic female carriers. In Generation IV there are 14 males with the trait, of a total of 52. In Generation VI there is but one male involved, of a total of six. Total males of Generations IV and V indicate it is a direct dominant characteristic, as 45% of the total have the trait. Considering the total number of males of these groups, we find in 32 males it is a direct dominant characteristic. In this 39 negative males, which indicates a dominant characteristic. This group happened to be very cooperative. The general pattern is that of a dominant inheritance. It does not appear to be sex-linked, because positive males produce negative and positive males and positive females produce positive and negative males, females with the trait, and negative females. The hereditary factor shows incomplete penetrance in the female, as demonstrated by asymptomatic females producing symptomatic males and females.

Family 2 (Fig. 2) is not related to the previous one, according to genealogical records dating back to 1813. The members of this family did not seek medical advice concerning diabetes insipidus nor had they sought it in the past. Owing to the inaccessibility of other members of the family, Gen. II, Nos. 4 and 5, and progeny of Gen. II, Nos. 5, 6, and 35 were the only patients studied.

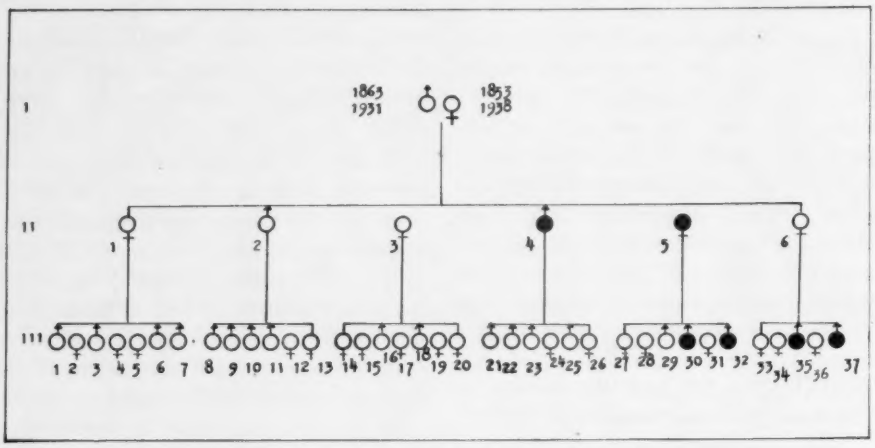


Fig. 2.—Family 2. Diabetes insipidus, extrapituitary type, primary (hereditary).

In the previous family the asymptomatic female carrier was studied and found to be normal in all respects except for a low serum albumin-globulin ratio. It was concluded that the inheritance was carried as a dominant factor with incomplete penetrance in the female. The second family substantiates this type of hereditary transmission.

A summary of the progeny of the second family is presented in Table 4. The original female (1863-1931) is assumed to be the carrier, as there is not an instance of any previous studies in which an asymptomatic male carried the trait. This summary shows a 1:1 ratio of positive males produced by positive parents. The females produced by positive parents seem to indicate that the inheritance is not dominant, but the low and incomplete penetrance in the female accounts for this deviation. These findings coincide with those of the previous study. In this small group the inheritance factor is a dominant factor with incomplete penetrance in the female. The incomplete penetrance in the female may be related to the female physiology.

Weil's group also shows the female carrier. Positive members of the family produced a total of 20 positive and 20 negative males. This gives a ratio of 1:1 and shows a dominant inheritance. The females produced by positive members, however, show 13 positive females, 29 negative females, and 1 female carrier. This gives a deviation of 7.5, which can only be accounted for by asymptomatic female carriers being classed as negative.

Most investigators have maintained that diabetes insipidus is transmitted as a dominant characteristic. Just ‡ criticized Liebmann,§ an early observer, for maintaining it to be a type similar to that of hemophilia. The present study indicates how this could be maintained in a small group studied. Just ‖ considered that the study by Weil was a clear case of a simple dominant characteristic. Ellerman ¶ and Bullock [3] were also of the same opinion. De Lange [1] noted that at

‡ Cited by de Lange.[1]
§ Cited by Chester and Spiegel.[5]
‖ Cited by de Lange.[1]
¶ Cited by de Lange.[1]

TABLE 4.—*Summary of Progeny of Family 2*

	Positive Male	Negative Male	Positive Female	Negative Female	Female Carrier
Positive male produced	0	4	0	2	0
Positive female produced	2	1	0	3	0
Carrier female produced	2	0	0	3	0
Original female produced	1	1	1	2	1
Total	5	6	1	10	1

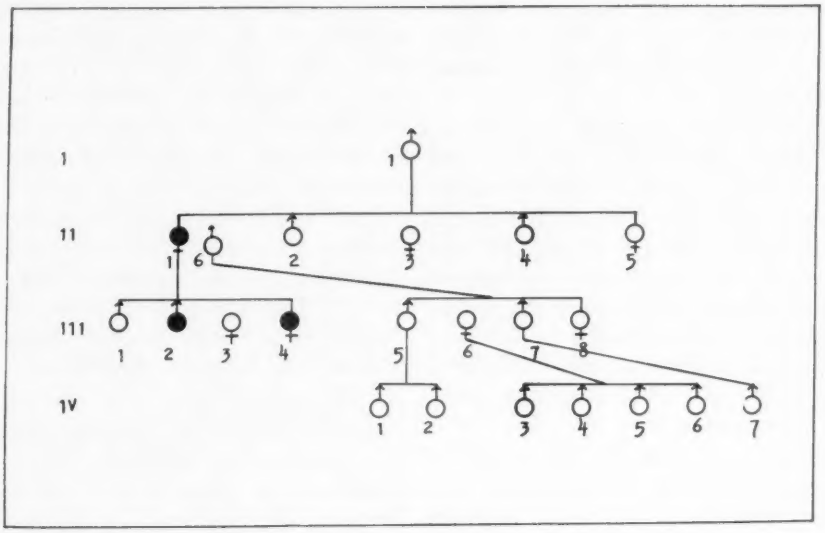


Fig. 3.—Family 3. Diabetes insipidus, pituitary type, primary (hereditary).

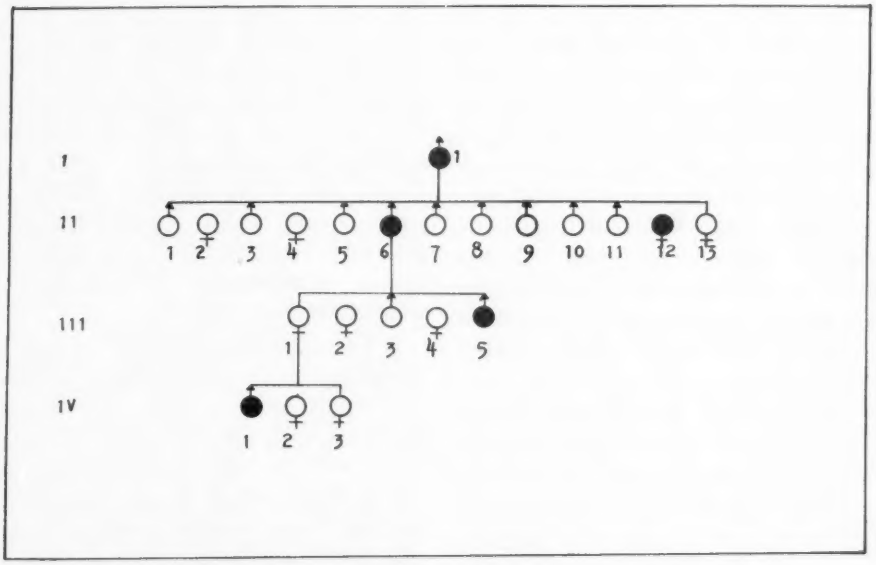


Fig. 4.—Family 4. Diabetes insipidus, pituitary type, primary (hereditary).

times the parents were free of the disease, as found in two examples in Weil's study. These asymptomatic parents were both females, which fits into the present concept of an asymptomatic female carrier.

In the present study of diabetes insipidus it is concluded that the inheritance factor in the primary (hereditary) extrapituitary type is not sex-linked and that it is a dominant inheritance with incomplete and even a low penetrance in the female.

2. Pituitary Type, Primary (Hereditary)

Two family histories of the pituitary type of hereditary diabetes insipidus are presented to demonstrate the method in which this hereditary trait is transmitted (Figs. 3 and 4). The family histories are too limited

to draw conclusions as to the type of hereditary trait, but they do demonstrate examples of how the trait is carried from generation to generation.

Family 4 (Fig. 4) shows the symptomatic cases to be present in four generations. The mother (Family 4, Gen. III, No. 1) did not have the symptoms of diabetes insipidus, as demonstrated in her case history. She had one boy with the condition and two girls who were symptom-free. This finding would indicate that the trait was carried as in the extrapituitary type, where it is carried as a dominant characteristic with incomplete penetrance in the female.

In summary, the pituitary type of hereditary diabetes insipidus can be carried as a dominant characteristic or as a dominant characteristic with incomplete penetrance in the female.

SECONDARY ETIOLOGICAL FACTORS

1. Extrapituitary Type

There have been many cases reported in which the extrapituitary type of diabetes insipidus resulted from infections. The commonest and perhaps the only type of infection to cause this type of diabetes insipidus is encephalitis. Many of these cases have been reported in the literature. No cases have been noted in the literature in which the extrapituitary type has followed or resulted from a neoplasm.

Experimentally, a lesion [16] that destroys the tuber cinereum or its pathway from the tuber downward results in a permanent polyuria refractory to treatment with posterior pituitary.

2. Pituitary Type

The etiological factor of the secondary type of pituitary diabetes insipidus has been somewhat confusing, because the destruction of numerous individual centers in the area of the pituitary gland have produced the disease.

Hann # thought it due to the destruction of the posterior lobe, with the anterior lobe still active. Richter * thought total removal of the pituitary produced temporary diabetes insipidus, whereas leaving the anterior lobe produced a permanent diabetes insipidus. Thus, an imbalance of the antidiuretic factor of the posterior lobe and the diuretic factor of the anterior lobe accounts for the symptoms.

The antidiuretic role of the posterior lobe is used as the basis of treatment. Replacing a deficiency results in relief of the symptoms.[26] The experimental disease may also be transmitted by the blood to another animal by cross circulation experiments.[18]

Other portions of the central nervous system have been involved in diabetes insipidus. The destruction of individual centers in the hypothalamus produces the symptoms if bilateral, but unilaterally it is ineffectual. Bilateral destruction of the supraopticohypophyseal system causes atrophy of the supraoptic nuclei of the posterior lobe and produces a permanent polyuria. This type is restored to normal by vasopressin (Pitressin). Interruption of the hypophyseal stalk produces the symptoms by cutting through the supraopticohypophyseal tract. This results in a hypertrophy of the gland cells about the pars tuberalis, which will later control the polyuria. Bourquin produced diabetes insipidus experimentally by cauterizing the floor of the third ventricle.

A brief consideration of the anatomy and physiology of this area facilitates an understanding of how these numerous lesions bring about the symptoms.[25] The pituitary is connected with the base of the brain just below the third ventricle by the pituitary stalk. It has been found in the experimental animal that fibers pass through the pituitary stalk from the supraoptic nuclei in the anterior part of the hypothalamus, to innervate the posterior lobe. The secretion of the antidiuretic principle by the posterior lobe is dependent on innervation through this tract. The system is a functional unit, and injury involving any area results in diabetes insipidus.

Other lesions have also produced the pituitary type of diabetes insipidus. Graham [10] relieved an increased spinal fluid pressure

Cited by MacCallum [16] and Wohl and Larson.[26]
* Cited by MacCallum.[16]

and relieved the symptoms which followed an accident. Dreyfus and many others reject the German theory that salt plays an etiological role. It has also been found that diabetes insipidus can be produced by denervation of the kidneys.[18] Jones,[25] in an analysis of 42 cases, shows the etiological basis to be, in order of frequency: tumor of pituitary, 26%; undetermined cause, 19%; chronic encephalitis, 16.6%; Hand-Schüller-Christian disease, 10%; syphilis and post-traumatic injury to the head, each 7%; tumor of the hypothalamus, 5%, and pituitary infarction, cerebrovascular accident, subarachnoid hemorrhage, and hypothalamic damage of undetermined etiology, all under 3%. Jones states that there is no history of an hereditary factor in the cases of undetermined etiology, which accounted for 19% of his 42 cases studied. (The inability to demonstrate a family pedigree in the history of an individual patient constitutes no valid objection to the theory of hereditary transmission. The example cited in this study in which the symptomatic patient is found after four preceding generations of asymptomatic female carriers may account for the inability to demonstrate the hereditary factor in many cases.) Measles and tuberculosis have also been etiological factors.†

An analysis of 22 cases of diabetes insipidus not known to be of hereditary type that respond to pituitary products and not previously reported shows the etiological basis as follows: post-traumatic, 2; associated with Banti's disease, 1; encephalitis, 1; Hand-Schüller-Christian disease, 1; arachnoiditis, 1; subsequent to medication (vermifuge), 1; metastatic lesion from a carcinoma of the breast, 1, and of unknown etiology, 14. Of the 14 of unknown etiology no hereditary factor could be obtained; however, many followed upper respiratory infections.

Necropsy reports are numerous for the pituitary type. Marenesco ‡ noted one of the hereditary type, but the patient had tuberculosis of the meninges, which may account for the pathological findings. Roberts § studied six necropsies; the etiological factors were not stated. In three cases the kidneys were atrophied and degenerated; in one case the granular tissue of the kidneys was entirely wanting; in the remaining case the kidneys were simply enlarged. Necropsy notes of a case in the present group are given in the section on morbid anatomy.

Fink ‖ in 107 necropsies found in 63% that the etiological factor was a tumor at the base of the brain or the posterior fossa; in 13% the etiological factor was a syphilitic lesion; in 6% the factor was a tubercular lesion; in 8%, an inflammatory process, and in 10%, a traumatic injury.

In summary, the etiological factor in the pituitary type of diabetes insipidus is primarily a deficiency of the antidiuretic principle of the posterior lobe of the pituitary. This deficiency appears to act on the kidney tubule either by a failure to resorb water preferentially or to avoid resorption of salt, or both.¶ Landale and Wajaman # think that extracts of the posterior lobe increase "hydrophilia" of the tissues and so reduce polyuria.

MORBID ANATOMY

1. Extrapituitary Type, Hereditary

On physical examination of patients no abnormality may be noted. Lipoid infiltration of the eyelids was not seen in the present study. There is in both families of the extrapituitary type a marked tendency to obesity.

Physical findings of the extrapituitary type, Family 1: A summary of the first family is noted in Table 5. One-half of the patients studied in detail were obese. In considering all of the patients interviewed and studied, obesity is a marked, almost constant finding. No marked or consistent congenital abnormalities were noted. Skull films were consistently normal (Fig. 5, Case 3; Case 7;

† References 13, 16, 18, and 19.

‡ Cited by Chester and Spiegel.[5]

§ Cited by Flint.[23]

‖ Cited by Jones.[25]

¶ References 17 and 26.

Cited by MacCallum.[16]

TABLE 5.—*Family 1*

	Sex, Age, and Family No.	Age at Onset	Physical Findings: Height, In.	Weight	Stature	Congenital Abnormality	Skull Film	B.M.R., %	Visual Fields	B. P.	Pulse Rate	Temp., F
1.	Female, 8 mo. Gen. IV, No. 13	1½ mo.	20	13 lb. 4 oz.	Normal	None	Normal	....	.....	.....	120	99
	At 19 mo.....		30¼	19 lb.	Normal	None	Normal	....	.....	.....	..	....
2.	Male, 11 yr. Gen. V, No. 187	First 10 days	58	118 lb.	Obese	None	Normal	0	Normal	100/68	84	99
3.	Male, 23 yr. Gen. IV, No. 87	First mo.	59½	157 lb.	Normal	Rt. inguinal hernia	Normal	−2	Normal	110/76	64	98
4.	Male, 27 yr. Gen. V, No. 38	Before 2 wk.	69¾	184 lb.	Normal	None	Normal	+12	Normal	110/82	72	98.4
5.	Male, 40 yr. Gen. V, No. 34 (7 mo. premature)	Before 2 wk.	66½	171 lb.	Obese	None	Normal	−1	Normal	130/76	72	98.6
6.	Female, 56 yr. Gen. III, No. 16	Birth	....	.....	Obese	None	.....	....	.....	136/80	84	98.8
7.	Male, 42 yr. Gen. IV, No. 80 (asymptomatic)	Whole life	56¾	146 lb.	Normal	None	Normal	....	Rt. part cataract	170/96	88	98.2
8.	Female, 36 yr. Gen. IV, No. 83	None	63½	183 lb.	Obese	None	Normal	−3	Normal	128/76	88	98.8
9.	Female, 64 yr. Gen. IV, No. 23	None	59	145 lb.	Obese	Bilateral hernias	Normal	−3	Normal	132/84	58	98.6

	Blood: Wassermann	B.U.N., Mg./100 Cc.	Uric Acid, Mg./100 Cc.	Sugar, Mg./100 Cc.	Chlorides, Mg./100 Cc.	Cholesterol, Mg./100 Cc.	Calcium, Mg./100 Cc.	Phosphorus, Mg./100 Cc.	Glucose Tolerance	Hgb.	RBC, Million	WBC	Diff. Count
1.	Parents Neg.												
2.	Neg.	12.8	3.2	84	478.5	260.0	10.0	4.8	Normal	97%	4.92	6,700	Normal
3.	Neg.	18.0	4.0	110	495.0	185.2	12.6	4.08	Normal	100%	4.81	13,600	Normal
4.	Neg.	17.8	5.3	116	462.0	173.0	9.2	4.0	Normal	92%	4.88	6,950	Normal
5.	Neg.	15.1	2.5	124	544.5	159.0	10.2	3.34	Normal	100%	5.03	4,300	Normal
6.	Neg.	23.4	...	...	.....	.....	....	...	.....	93%	5.80	7,400	Normal
7.	Neg.	40.0	2.8	186	495.0	250.0	9.0	3.5	.....	72%	3.96	10,400	Normal
8.	Neg.	17.4	2.8	90	445.5	257.0	9.1	3.1	.....	80%	4.12	6,900	Normal
9.	Neg.	28.0	...	111	.....	.....	....	...	.....	....	....	.....	.....

TABLE 6.—*Summary of Blood and Urine Findings in Family 1*

Sex, Age, and Family No.	Blood				Urine									
	Total Protein	Albumin	Globulin	A/G Ratio	Hours of Concentration	Specific Gravity	Cc. in 24 Hr.	Specific Gravity	Color	Reaction	Albumin	Sugar	Microscopic	Total NaCl, Gm.
Normals														
Male, 65 yr. Gen. IV, No. 12	7.6	4.0	3.6	1.11	9.5	1.016	.....	1.016	Light straw	Acid	Neg.	Neg.	Rare pus	....
Male, 52 yr. Gen. III, No. 81	6.8	3.8	3.0	1.27	20	1.026	.....	1.026	Light yellow	Acid	V.f.tr.	Neg.	Rare crystals	....
Female, 68 yr. Gen. III, No. 75	6.75	3.80	2.95	1.28	23	1.026	.....	1.026	Light yellow	Acid	V.f.tr.	Neg.	Rare pus	....
Male, 72 yr. Gen. III, No. 9	6.5	3.6	2.9	1.24	12	1.021	.....	1.021	Light yellow	Acid	Neg.	Neg.	Crystals, few bact.	....
Female, 37 yr. Gen. IV, No. 68	7.64	4.77	2.87	1.66	13.5	1.021	.....	1.021	Light yellow	Acid	Neg.	Neg.	Rare pus, amorphous	....
Male, 44 yr. Gen. IV, No. 65	8.00	4.03	3.48	1.3	16	1.024	.....	1.024	Light straw	Acid	Neg.	Neg.	Crystals	....
Female, 42 yr. Gen. IV, No. 92	8.52	3.70	4.82	0.77	14	1.015	.....	1.015	Light straw	Alk.	Neg.	Neg.	Many pus, few RBC	....
Female, 46 yr. Gen. IV, No. 11	7.9	4.7	3.2	1.47	12.5	1.014	.....	1.014	Straw	Acid	Neg.	Neg.	Rare pus	....
Asymptomatic														
Female, 75 yr. Gen. III, No. 41	9.6	3.9	5.7	0.7	19	1.020	1,880	1.006	Light straw	Acid	Neg.	Neg.	V. rare pus, v. rare RBC	5.26
Female, 64 yr. Gen. IV, No. 23	6.2	3.14	3.06	1.02	18	1.007	2,200	1.006	Light straw	Alk.	Neg.	Neg.	Amorphous crystals	9.41
Female, 43 yr. Gen. IV, No. 192	8.30	4.16	4.14	1.00	17.5	1.022	2,550	1.009	Yellow	Acid	Neg.	Neg.	Occ. pus, occ. epi.	12.5
Female, 37 yr. Gen. IV, No. 83	7.7	3.68	4.02	0.91	18	1.017	2,060	1.010	Amber	Acid	V.f.tr.	Neg.	V. rare cast	9.18
Female, 45 yr. Gen. IV, No. 191	7.88	3.85	4.03	0.95	22	1.019	1,814	1.007	Light yellow	Acid	Neg.	Neg.	Occ. pus	10.26
Symptomatic														
Female, 6 mo. Gen. VI, No. 13	....	....	....	....	..	.....	1,970	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	....
At 19 mo.	....	....	....	....	..	.....	3,062	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	....
Male, 11 yr. Gen. V, No. 187	8.0	3.5	4.5	0.77	..	.....	9,895	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	11.4
Male, 13 yr. Gen. V, No. 209	8.12	4.16	3.96	1.05	..	.....	10,086	1.001	Water-clear	Acid	Neg.	Neg.	Neg.	8.3
Male, 23 yr. Gen. IV, No. 87	7.0	4.16	2.84	1.47	..	.....	14,800	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	25.00
Male, 27 yr. Gen. V, No. 38	9.63	4.69	4.94	0.95	..	.....	16,050	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	19.50
Male, 34 yr. Gen. V, No. 36	6.5	2.93	3.57	0.82	..	.....	15,775	1.000	Pale yellow	Acid	Neg.	Neg.	Neg.	25.96
Male, 40 yr. Gen. V, No. 34	7.00	3.44	3.56	0.93	..	.....	13,120	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	19.41
Male, 42 yr. Gen. IV, No. 80	6.8	3.6	3.2	0.90	..	.....	3,580	1.002	Water-clear	Acid	Neg.	Neg.	Neg.	7.66
Female, 57 yr. Gen. III, No. 16	....	....	....	....	..	.....	15,550	1.000	Water-clear	Acid	Neg.	Neg.	Neg.	19.25

Figure 5 (Case 3).

Figure 6 (Case 3).

Case 23, asymptomatic female carrier). Visual fields were normal in the family studied [27] (Table 5). Best [19] states that an elevation of the basal metabolism rate is common in this disease. These rates were consistently normal in this group. A tendency to bradycardia [8] and temperature lability has been noted previously and is substantiated in the present study. Intravenous pyelography in symptomatic cases (Fig. 6, Case 3) showed megaureter and rapid elimination of dye with a very large bladder. Normal ureter and bladder were noted in the asymptomatic female carrier (Case 23). An enlarged, dilated stomach was noted in Case 10.

The findings at necropsy of a male patient (Case 2), aged 6 years, were normal but for the kidneys, which, except for fetal lobulation, were normal in size and macroscopic appearance. The renal pelvis was somewhat dilated. The urinary bladder wall was thickened and trabeculated. The ureters were markedly dilated, as was noted in other cases.

The pathological summary of the abnormal findings and the endocrine system are given in detail on Case 28 (Family 1) because I believe that it is the first study made of the extrapituitary type of diabetes insipidus.

General Description.—The body is that of a white male infant measuring 53 cm. in length and weighing 4325 gm. The skin is dry and slightly cyanotic. The anterior fontanel is open and is cross shaped, measuring 5 cm. anteroposteriorly and 4 cm. transversely. The tongue has a hemorrhagic crusted surface. The dorsa of the hands are markedly edematous and show recent and old puncture marks with surrounding ecchymoses. There are similar needle marks in the regions of the thighs and over the heels. There is an upper abdominal incision which measures 7 cm. in length and follows the right costal margin. The testes are not in the scrotum. There is a large right abdominal mass. There is a needle mark over the fifth lumbar vertebra in the midline and many needle marks with surrounding ecchymoses over the buttocks.

Primary Incision.—The subcutaneous fat is moderately abundant, measuring up to 9 mm. in the midline. There are many black sutures in the right upper quadrant in the region of the incision. The bladder is markedly enlarged, extending up to the umbilicus, and contains 45 cc. of clear urine. The liver is markedly enlarged, extending 5 cm. below the costal margin in the right midclavicular line, 4.5 cm. below the xiphoid process in the midline, and 3.5 cm. below the left costal margin in the midclavicular line. The vein of the ligamentum teres is closed. The urachus is present as a narrow cord measuring 1 mm. in diameter.

The thoracic cavities are dry. The anterior surfaces of the lungs show many small hemorrhages measuring up to 3 mm. in diameter.

The pericardial sac and the heart appear normal.

Lungs.—The left lung weighs 31 gm. (normal, 30 gm.) and is light pink and well aerated in most portions, but on the posterior aspects, most marked in the lower lobe, are many irregular purple areas which are slightly depressed and tend to follow lobular distribution. On the posterior surface of the inferior lobe is an oval, indefinitely outlined,

raised area measuring 2×1.5 cm. and rising 0.8 cm. from the surface. On the center of this is a sharply demarcated yellow patch which is slightly irregular in form and measures 1 cm. in diameter. Adjacent to it is a smaller, similar yellow patch measuring 3×1 mm. On section, this yellow patch is seen to be approximately hemispherical in shape and to extend 4 to 5 mm. in depth. It is surrounded by a dark indefinitely outlined zone measuring 2 mm. in diameter. A few purple areas measuring up to 5 mm. in diameter are present in both lobes.

The right lung weighs 33 gm. (normal, 35 gm.) and resembles the left lung, but the blue areas are more extensive, occupying approximately one-sixth of the total surface.

Gastrointestinal Tract.—The mucosa of the esophagus shows a few petechial hemorrhages measuring up to 3 mm. in diameter. The rugae are more prominent than usual, and the wall near the cardia measures 2 mm. in thickness. Near the pylorus the wall is markedly thickened and has a cartilaginous appearance. Here the muscularis measures 3 mm. in thickness and the mucosa, 1 mm. At the pylorus a small inpouching of the mucosa is present, which is tied by a suture. The small bowel and colon are normal.

Gall Bladder and Biliary System.—The gall bladder, liver, spleen, and pancreas present no significant abnormalities.

Genitourinary System.—The right kidney weighs 17 gm. (normal, 20 gm.); the left weighs 22 gm. (normal, 19 gm.). Fetal lobulation is present. On section the cortex measures 3 mm. in thickness. It is uniform and is paler than normal. The pelves appear normal. The ureters are moderately dilated, measuring 6 mm. each in circumference. The bladder when opened measures 6×7 cm., and the wall measures 1 to 2 mm. in thickness. The rugae are not as prominent as normal, and the mucosa is pale. The organ contains 65 cc. of clear urine. The prostate appears normal. The testes appear grossly normal and lie within the inguinal canals.

The adrenals weigh 5 gm. together. Their external configuration is normal. On section they show yellow cortices, which measure 1 mm. in thickness, and well-preserved medullae.

The thyroid weighs 1 gm. It is symmetrical and on section shows light pink parenchyma containing moderate amounts of colloid.

The thymus is smaller than normal. Its development is commensurate with the age of the subject.

The pituitary measures 1 cm. transversely, 0.7 cm. anteroposteriorly, and 0.4 cm. in depth. It appears grossly normal.

The brain (fixed) weighs 750 gm. (normal, 516 gm.). Its contours appear normal. Multiple sections reveal no abnormalities.

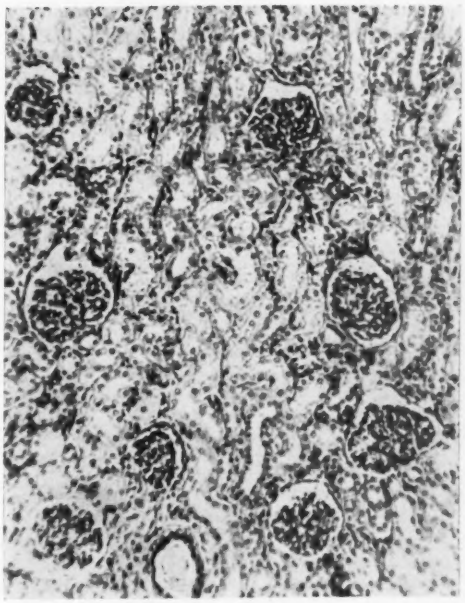


Figure 7 (Case 28).

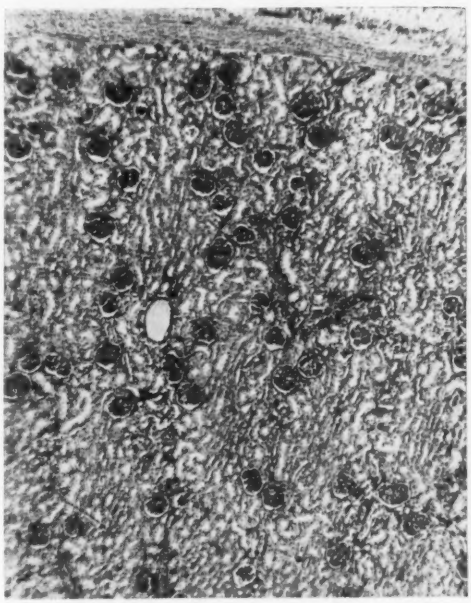


Figure 8 (Case 28).

Bacteriology: Lung abscess with Pseudomonas (predominating) and Gram-positive cocci (type not determined).

Genitourinary System.—Kidney: The glomeruli are of the infantile type. The tubule cells show minimal to slight foaminess of their cytoplasm.

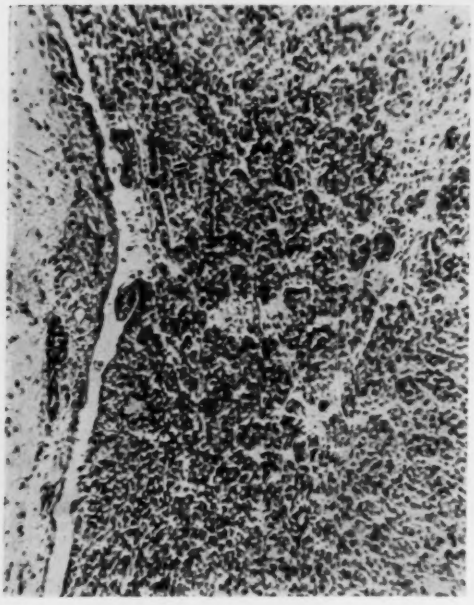
The lumens contain small amounts of granular red-staining matter. Rare tubules show marked dilatation and contain intensely staining green masses. The pelvis appears normal (Figs. 7 and 8).

Bladder: The muscularis shows moderate edema.

Testis: The tubules show slight lumen formation but no differentiation of the elements. The rete testis and vas appear normal.

Figure 9 (Case 28).

Figure 10 (Case 28).



Endocrine System.—Pituitary: The posterior lobe occupies about one-third to one-half of the area. Its cells are slightly larger than usual. The anterior lobe shows palisade arrangement of its cells in the posterior portions, suggesting compression by the posterior lobe. The anterior lobe shows about equal numbers of chromophobes and acidophiles, with a smaller number of basophiles (Figs. 9, 10, and 11).

Thyroid: One lobule is of the fetal type. The other lobules show small to medium sized acini with tall lining cells and abundant homogeneous colloid with marked marginal scalloping.

Adrenal: Two small masses of cortical tissue are present outside the capsule. The cortex is almost

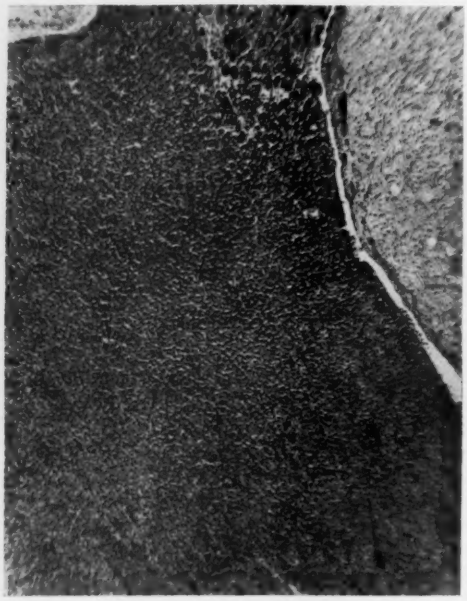


Figure 11 (Case 28).

devoid of lipoid. It shows an inner fibrous zone which contains cells with pyknotic nuclei and pale-staining foamy cytoplasm and cells which resemble large monocytes. The medulla is well preserved and appears normal.

Thymus: A serous membrane covers one surface. The lobules do not show division into cortex and medulla. Relatively small numbers of lymphocytes are present, and most of them show irregular deeply staining nuclei.

Hemopoietic System.—Accessory spleen: A minute accessory spleen, histologically resembling the spleen, is represented.

Central Nervous System.—Midbrain: Severe perineuronal and generalized edema is present.

Many areas of demyelination are present. The neurones show shrinkage and hyperchromatism of cytoplasm and nuclei. There is proliferation of the spindle cells of the arachnoid membrane.

Insula and Putamen: Similar to the midbrain. Perivascular and scattered areas in which the brain substance stains vary intensely and shows deposition of deeply red-staining homogeneous matter are present. Most such areas show infiltration of glia cells.

Cerebellum: Similar to the midbrain.

The physical examinations and laboratory findings in the second family are summarized in Table 7. Obesity was noted in two of the four patients with the primary type. Two positive males (brothers) had mottled teeth; however, this is a common finding in the area of their nativity. The skull films were consistently normal, as in the first family. An elevation of the temperature and pulse were noted. Intravenous pyelography showed rapid elimination of the dye and very large bladders in the primary type. The total serum proteins in these cases were normal, as compared with the first family, in which there was frequently an inversion of the A/G ratio with a normal total protein.

TABLE 7.—*Summary of Family 2*

Case No.	Sex	Age, Yr.	Urine Output, Cc./24 Hr.	Specific Gravity	Concentration Time, Hr.	Specific Gravity	Stature	Temp., F	Pulse Rate	Total Serum Protein, Gm.	A/G Ratio
Symptomatic Family Members											
29	M	51	20,500	1.000	2	1.000	Slender	98	64	4.54	3.2
30	F	45	8,424	1.000	8	1.000	Obese	99	102	5.68	1.43
31	M	16	18,450	1.000	3	1.000	Obese	100.2	100	6.72	3.62
32	M	8	9,504	1.000	3	1.000	Normal	100.4	112	5.71	3.13
Asymptomatic Family Members											
	F	23	1,243	1.010	18	1.018	Normal	98	100	7.4	2.04
	F	15	1,400	1.008	16	1.018	Normal	98	104	6.08	2.19

2. Pituitary Type, Hereditary

Examination of the patients with the pituitary type may manifest no abnormality. It may, however, demonstrate abnormalities consistent with the etiological factor, as in cases caused by pituitary tumors, encephalitis (Case 23) or syphilis, Hand-Schüller- Christian disease, Banti's disease, or trauma.

In this series of 21 cases there are 14 females and 7 males, which is an opposite sex ratio to that found in the hereditary extrapituitary type.

BLOOD STUDIES

1. Extrapituitary Type, Hereditary

The serologic tests for syphilis, blood urea nitrogen, uric acid, sugar, chlorides, cholesterol, calcium, and phosphorus were found to be consistently normal except in cases complicated by other disease processes (Table 5). It has been stated that diabetes mellitus and diabetes insipidus are not found in the same patient. Both have been found in two patients studied (Cases 8 and 19). Hypertension and chronic nephritis, along with diabetes mellitus and advancing years, brought about diminution of the symptoms of diabetes insipidus in Case 8.

The only abnormality was found in the inversion of the albumin-globulin ratio in five of the seven patients in Family 1. A comparison is made in Table 6 of the findings of normal members of the family, proved female carriers, and symptomatic members. The albumin-globulin ratio was normal in the normal members except in one case, which happened to be seven days postpartum. In the proved female carriers the albumin-globulin ratio was inverted in three of five cases studied, and in the remaining two it was 1.00 and 1.02, showing that they were not exactly normal in this respect. In the symptomatic members the ratio was inverted in five of seven cases, and in the remaining two cases it was 1.05 and 1.47.

Although the total plasma protein was normal, there was a marked tendency toward

inversion of the albumin-globulin ratio in the asymptomatic female carrier and the symptomatic members studied in this group. This finding may be of some aid in determining which females of an involved family are carriers of the trait.

Table 6 clearly shows that the normal family members and the asymptomatic female carriers had normal urinary concentrating ability. In the one instance the asymptomatic female (Case 24) had a concentration of only 1.007 after 18 hours, and it is also observed that she had a history of hypertension and a previous cerebral vascular accident, which may account for the decreased urinary concentrating ability.

Blood studies in the second family do not substantiate the findings in the first family concerning the serum protein and A/G ratio (Table 7).

2. Pituitary Type, Secondary

Blood studies are related to the etiological factors as in syphilis, Hand-Schüller-Christian disease, and Banti's disease.

AGE AND LIFE EXPECTANCY

1. Extrapituitary Type, Hereditary, Family 1

The onset is often noted at birth, as in the case of the patient (Case 7) who was born prematurely at 7 months, with symptoms noted by the mother in the first two weeks. (Gee * also noted the onset of symptoms at birth; Chester and Speigel [5] state that it is never found at birth.) The frequency with which the symptoms are noted at birth in this group is probably due to the fact that it is common and expected in the family. Marañón [7] reported 35 cases observed personally, of which 75% showed symptoms before 10 years of age. Deluca † reported a case at 3 months and thought it to be the earliest mentioned in literature. Weil stated that the family could determine by 6 months of age if the child was going to be a "water drinker." de Lange [1] stated that most patients started to have symptoms at one year of age.

Several observers have noted decrease in symptoms with advancing years. Blotner [13] noted improvement in a patient at the menopause. Cohabitation and advancing years have decreased enuresis, as noted in the family of Gen. IV, No. 23, in Family 1.

The symptoms remain unabated in this group with advancing years. One patient (Case 8) had decreased symptoms after developing diabetes mellitus, hypertension, and nephritis.

Weil observed that if the patients reached puberty they lived a normal span of life. At one time Weil had 12 patients with diabetes insipidus in one room. The youngest was 2 years old, and the oldest, 76. Weil had three patients who lived 83, 87, and 92 years, respectively.

The present study demonstrates the increased early mortality rate in the first family. Of 679 in the family, 58 died before 3 years of age (8.5%). Of those who died before 3 years of age there were 26 males, 31 females, and 1 premature of unrecorded sex. Only two of those who died before the third year were known to have had diabetes insipidus. It is likely, however, that many of those who died before 3 years of age had diabetes insipidus, which could account for the increased early death rate.

Of those who had diabetes insipidus and reached 3 years of age, the average span of life was 46.6 years. Of these 14 persons, 9 lived past 50 years, the oldest being 79 years of age. Three died after surgical operations at the ages of 7, 21, and 29 years. One died after an accident at the age of 20 years. None of these deaths before 50 years could be attributed to diabetes insipidus except as a complication of surgery. At present, the oldest patient alive is a male, 59 years of age, and the youngest is a female 19 months old (6 months of age when this study was begun).

2. Pituitary Type, Secondary

The age of onset and life expectancy would be related to the etiological factors, which would show the age of onset to be mostly after the third decade of life and the life

* Cited by de Lange.[1]

† Cited by Marañón.[7]

expectancy to be shortened by the disease process causing the disease.

The present study of 22 cases of this type shows the youngest to be a girl 2 years of age and the oldest a woman 52 years of age. The average age at examination was 28.80 years, which is younger than that shown in previous studies.

SYMPTOMS

Chester and Speigel [5] have classified the symptoms into two groups, because, as they stated, Weil pointed out that the kidneys in infants play a comparatively minor role in regulation of water exchange. It is at 2 years of age that children's kidneys take over the water balance, and up to this time 17% to 56% of the water of an infant is eliminated through the skin (in older children 15% to 32% of fluid intake is eliminated through the skin). At about 2 years of age the kidneys add the function of regulation of water balance to that of excretion of metabolic products.

Symptoms in Infancy.—Polyuria is present at birth. In large families where the disease is common and expected it is naturally noted earlier than where uncommon. The parents observe that the child cries excessively and will be quieted only by water, as Gee ‡ found. McIlbraith § reported diarrhea. Also noted was elevation of temperature in this group, undoubtedly due to dehydration. Slow growth during the first year of life was found with Gen. VI, No. 13 (Case 1). A "sweet" measles odor to the breath was noticed by one parent in this group. Dissatisfaction with milk was a very common finding. Infants may vomit even water if thirst becomes excessive. There is a marked susceptibility to pyelitis and pyuria. The ability of the infant to retain large amounts of water is noted.

Symptoms in Childhood and Adult Life.—It has been noted that enuresis is very common and may extend until the late teens or until cohabitation, at which time it usually ceases. Nocturnal and diurnal polyuria symptoms of primary type, according to Weil, are severest in early adult life. There are cases in this group, however, in which a male patient around 70 years of age emptied a waterbucketful each night. Drinking of alcohol is very uncommon, and Pain is the only one who reported such a case. The patients of this group complained of excessive thirst lasting three to four days if another source of water supply was used. The adults of this group state that going without water for over two hours causes emotional instability. One patient cried during an intravenous pyelogram, only to regain control of his emotions after several glasses of water. Other symptoms of thirst noted are epigastric pain, hunger, and a sensation of a rise in temperature developing in the afternoon, with the lips having the feeling of "fever blisters" forming. A morning cough with the production of a thick, tenacious, mucoid material has been noted. A sweet odor of breath is marked when thirst is present. The sensation of a swollen tongue and thickness of speech have also been noted during thirst. Apparent fever has been noted at times, but it has always found to be normal on examination. The pregnant female may have diminution or aggravation of symptoms. It has been noted by several of this group that if they are extremely thirsty water first causes nausea and even vomiting until large amounts have been taken. A choking sensation during thirst has been noted. Many patients have stated that quenching their thirst with cold water gives them the greatest satisfaction in life. Their habits center in their disease. The patients state that on entering any new lodging, if only for a night, their first thoughts are of the whereabouts of the water source and of a place to eliminate the water taken.

COMPLICATIONS

Weil reported that if the patient with diabetes insipidus survived the first few years the chances were good that he would live the normal life expectancy. In the first family, this was also noted (before Weil's article

‡ Cited by de Lange [1] and Bullock.[3n]

§ Cited by Chester and Spiegel.[5]

was read), and it was found that 8.5% died before 3 years of age. In Family 1 febrile illnesses, operations, and infection have not been tolerated well. Few have survived operations. This brings up the factor most important to the patient. The patients have been found to keep the information from physicians and friends. The psychic reaction to the disease is not normal, especially where a strong hereditary factor is present. One patient kept the knowledge of her disease from the hospital attendants by drinking water from the hot water bottle. One drank the water out of the flower vases and developed diarrhea which later resulted in death. One suffered a fractured skull from a blow incurred while staying at a drinking fountain too long while others waited impatiently.

In Family 1 obesity is common among those involved. Diabetes mellitus is also common in the family, which may account for some of it being present along with diabetes insipidus. Hypertension is noted in several of the female carriers.

In the second family, as in the first, nervousness is marked.

In cases of diabetes insipidus due to secondary etiological factors the complications are related to the disease process.

The complications when the diabetes insipidus is secondary to other pathology are related to the etiological factors.

DIAGNOSIS

Brown and Rynearson [15] advocate that the suspected person go as long as possible, up to the point of discomfort, without water, at which time the specific gravity of the last urine sample should not exceed 1.008. They noted, however, that in one of their patients whose case was typical in all respects, and whose symptoms were also relieved by posterior pituitary, the urine had a specific gravity of 1.016.

The findings in Table 10 are based on the foregoing test. It is noted that the members of normal families exceed these standards. They are able to concentrate the urine over 1.008 specific gravity. It is also noted that the asymptomatic female carrier meets these requirements except in the one case accounted for by hypertension. The volume in 24 hours was below 3000 cc. in the asymptomatic female carriers and was above 3000 cc. in all the symptomatic ones. All symptomatic patients were markedly above the 3000 cc. output except in the one case in which diminution of symptoms accompanied advancing years, diabetes mellitus, chronic nephritis, and hypertension.

The symptomatic patients state that they desire excessive salt. The average sodium chloride output for the symptomatic patients was 17.06 gm. in 24 hours, while the asymptomatic females had an average output of 9.32 gm. in 24 hours.

The findings in the blood protein determinations may be of some aid in diagnosis, as previously discussed.

TREATMENT

This group of patients is so accustomed to the inconvenience of the disease that only one had sought medical relief. Best [19] states that pituitary products are the only means available for the control of diabetes insipidus and are not effective in all cases. Snell and Rowntree have found that diabetes insipidus which results from encephalitis does not respond to pituitary treatment. One patient demonstrated a severe reaction on being treated with vasopressin (Pitressin) tannate (pituitary type, secondary, Case 44).

Farini || and Van der Velden ¶ independently first used the extract of pituitary in the treatment of diabetes insipidus, in 1913.

Blumgart # first used a solution of pituitary as a nasal spray, in 1922.

Audrey, in 1924, showed the symptoms of diabetes insipidus could be controlled by 50 mg. of the dry powder of the posterior lobe of the pituitary three times daily used as a snuff.

Green and January,* in 1940, found that vasopressin tannate in oil given subcutaneously had an effect lasting from 30 to 82

|| Cited by Canelo and Lisser [14] and Jones.[25]
¶ Cited by Chester and Spiegel [5] and Jones.[25]
# Cited by Canelo and Lisser.[14]
* Cited by Blotner.[13]

hours. Stephen's patient found that one injection lasted 96 hours. In this type, 5 pressor units of vasopressin tannate is suspended in 1 cc. of oil. It has been found that 1 cc. every 48 to 60 hours is sufficient to relieve the symptoms of polydipsia.

The disadvantage of posterior pituitary U.S.P., is that it lasts but a few hours. It is often necessary to give it four times daily. It has caused intestinal cramps and diarrhea (noted in one of these patients) as well as headaches, palpitations, and pallor.

Camelo and Lisser compared the relative costs of the foregoing treatments and found that vasopressin costs $15.30 per month; obstetrical posterior pituitary U.S.P., $11.25 a month, and posterior pituitary powder as nasal insufflation, but $4.00 a month. (The powder has been used effectively in some patients by my associates.) The ease of administration and low cost make it the desirable method of treatment. In this study, 40 mg. was routinely given four times daily.

Table 8 reveals the discouraging results with all methods of treatment in the first family. None of the foregoing methods has been beneficial. One patient thought he noted less thirst, but on examination found he had actually increased his output. Two members of the family (Gen. V, No. 9, and Gen. V, No. 36) have been treated recently with no clinical benefit. It is not possible to measure the result accurately. It must be remembered that this is a study of people who are of the upper middle class and working and who are not seeking medical attention. These studies took long periods of time; vacations were used to measure carefully the results. Cooperation as to treatment was very conscientious in all instances. Results were discouraging for all concerned, and further cooperation with such results could not be requested.

Table 9 reveals the discouraging results with all methods of treatment in the second family.

The treatment of the pituitary type of diabetes insipidus is related to the etiological factor. Hand-Schüller-Christian disease has been reported to give a good response to

TABLE 8.—*Results of Treatment in Family 1*

Sex, Age, and Family No.	Type of Treatment	No. of Days	Average Output/ 24 Hr., Cc. (Intake)	Salt Output/ 24 Hr., Gm.	Sp. Gr.	Reaction	Color	Sugar	Albumin	Micro.
Female, 6 mo.										
Gen. VI, No. 13	None	2	1,162	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
At 10 mo.	None	1	2,855	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
At 19 mo.	None	1	3,062	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Male, 11 yr.	None	2	10,155	11.4	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Gen. V, No. 187	Post. Pit. Pwd., U.S.P., 40 mg. q.i.d.	8	10,429	7.2	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
	Vasopressin tannate in oil, 2 cc. daily	18	9,745	7.99	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Male, 23 yr.	None	5	14,435	25.0	1.000	Acid	Pale green	Neg.	Neg.	Neg.
Gen. IV, No. 87	Obs. Pit. inm. X.T.I.D.	4	14,627	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
(cramps)	Post. Pit. Pwd., U.S.P., 40 mg. q.i.d.	5	14,730	18.11	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Male, 27 yr.	None	2	15,800	19.50	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Gen. V, No. 38	Post. Pit. Pwd., U.S.P., 40 mg. q.i.d.	4	21,943	26.3	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Male, 40 yr.	None	7	9,346	19.41	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
Gen. V, No. 34	Obs. Pit., 1 cc.	2	14,420	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
	Vasopressin tannate in oil, 2 cc. daily	4	13,200	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.
	Post. Pit. Pwd., U.S.P., 40 mg. q.i.d.	4	16,250	.....	1.000	Acid	Water-clear	Neg.	Neg.	Neg.

TABLE 9.—*Treatment Summary in Diabetes Insipidus, Extrapituitary Type (Hereditary), Family 2*

Case No.	Type of Treatment	Days	Symptoms	Urine: Before Treatment, Cc./24 Hr.	Urine: Before Treatment, Specific Gravity	Urine: After Treatment, Cc./24 Hr.	Urine: After Treatment, Specific Gravity
29	1 cc. vasopressin tannate in oil (5 pressor units)	14	Slightly diminished thirst	20,500	1.000	15,600	1.000
30	1 cc. vasopressin tannate in oil (5 pressor units)						
	0.48 hr.	7	No change	8,424	1.000	7,700	1.000
	0.24 hr.	7	Diminished thirst, no nocturia	.....	.....	6,900	1.000
	0.12 hr.	2	Throbbing headache, moments of unconsciousness	.....	.....	6,350	1.000
	No treatment for 60 days; no change			.....	.....	6,200	1.000
	No change in degree of thirst after taking U.S.P. posterior pituitary (40 mg. q.i.d.) for 7 days						
31	1 cc. vasopressin tannate in oil (5 pressor units)						
	0.48 hr.	7	No change	18,450	1.000	11,450	1.000
	0.24 hr.	7	Diminished thirst, no nocturia	.....	.....	9,400	1.000
	0.12 hr.	2	No change	.....	.....	7,700	1.000
	No treatment for 60 days; no change			.....	.....	11,600	1.000
	No change in degree of thirst after taking U.S.P. posterior pituitary (40 mg. q.i.d.) for 7 days						

roentgen irradiation. When syphilis is the etiological factor, antisyphilitic treatment is indicated and often relieves the symptoms.

Families 3 and 4 (Figs. 3 and 4) responded well to treatment, as noted in the case histories. Case 34, pituitary type, secondary, shows good response to vasopressin tannate, which has effect for varying lengths of time but usually over 30 hours. Increased urination is noted before the onset of thirst, and this sign is used as the indication for more medication. Although the patient preferred medication by the use of posterior pituitary powder by nasal insufflation, the untoward symptoms of marked cough, itching, and vomiting made this type of medication less desirable. Case 35, pituitary type, secondary, clearly demonstrates severe water intoxication, with coma resulting from two injections of vasopressin tannate. This is a case of postencephalitis, which often does not respond to posterior pituitary products. Cases 42 and 43, pituitary type, secondary, demonstrate the ideal response to treatment. Case 45 of the same group demonstrates relief of symptoms but a complication of treatment. The allergic response and its treatment is discovered in Case 44 of the same group.

It is noted that relief of symptoms occurs within five minutes of the time of injection of the pituitary products and before water has been consumed. The fluid balance of the body is apparently not related to the thirst sensation under these circumstances.

The dramatic results and the various complications and symptoms of the different types of treatment are well outlined in Table 10.

Another type of treatment may be of use in the treatment of diabetes insipidus, as described in the following study.

TREATMENT OF DIABETES INSIPIDUS BY THE USE OF LOZENGES OF POSTERIOR PITUITARY

The rational treatment of diabetes insipidus is based upon a thorough study of the etiological factor. It must be understood that the etiological factors are numerous and because of these numerous factors the treatment varies greatly.

In the pituitary type of diabetes insipidus the symptoms of the disease are dramatically relieved by the administration of the pituitary products in one form or another. Herein lies the danger of relieving the symptoms while a disease process progresses.

The present study was undertaken to determine the value of lozenges of the posterior pituitary products in relief of the symptoms.

Problems in the Present Treatment.—The disadvantage of posterior pituitary U.S.P.,

is the short duration of its action, necessitating numerous subcutaneous injections daily.

The dry powder of the posterior pituitary used as a nasal snuff lasts but a few hours. It is the most economical and the most desirable form of treatment. It does have the marked disadvantage of being very irritating to the nasal mucosa, and in many instances this form of treatment is impractical. The medication causes sneezing and protracted coughing bouts.

Vasopressin tannate in oil is expensive. It has the disadvantage of being given by hypodermic injections. Its duration of action varies, and the potency of the ampules varies greatly. Its action is often great for many hours, and suppression of urination for several hours makes urinary tract infections more likely.

Case Studies in Treatment with Lozenges of Posterior Pituitary, 30 mg. Each.—Four patients with known diabetes insipidus cooperated in this study. In each instance they presented problems in treatment.

CASE 44.—The patient was a 52-year-old graduate nurse with no family history of diabetes insipidus. The onset of her symptoms appeared after an upper respiratory infection.

Skull films and various other methods of diagnosis failed to prove the etiological factor. Before any medication was tried on this patient she averaged 5136 cc. urine output each 24 hours. She was treated with vasopressin tannate in oil, which gave immediate relief of the thirst symptoms, but she developed such severe headache, and localized reactions about the site of injection, that this form of treatment had to be discontinued. She later proved to be sensitive to aqueous pituitary products, and desensitization had to be carried out before vasopressin tannate could be used in the treatment of the disease. Pituitary powder was far too irritating, even in minute quantities, to use as a method of treatment.

CASE 42.—The patient was a 37-year-old housewife who had had numerous operations. At 16 years of age she had had an appendectomy, following which she noted the onset of polyuria and polydipsia which persisted until treatment was started, at 37 years of age.

Skull films and other tests failed to reveal the site of the lesion. Her average urine output during hospitalization before treatment was 11,000 cc. each 24 hours.

This patient was first started on posterior pituitary, which she found too rapid and too pronounced in its action and too short in the duration of its effect. She received good results with the pituitary powder used as a nasal snuff.

CASE 40.—The patient was a 35-year-old white obese woman. She noted the onset of obesity and thirst at the same time. They were gradual in onset but progressive. X-ray films of the skull have been persistently normal for four years while she has been under treatment, and no site of lesion has been proved.

Over a 72-hour period her urine output was 18,500 cc. each 24 hours, before treatment was instituted.

The patient was first tried on posterior pituitary powder as a snuff, but owing to the marked irritation this type of treatment had to be discontinued, and at present the patient takes vasopressin tannate in oil.

CASE 45.—A 40-year-old white obese woman first noted the onset of thirst following the delivery of her first child, when she was 28 years of age.

X-ray examinations have been negative, and no proved site of the lesion has been demonstrated.

Her output of urine at the onset, before treatment was instituted, was 20 pints (about 10 liters) each 24 hours.

Her treatment was started with posterior pituitary and later was changed to vasopressin tannate in oil, which caused epistaxis and pitting edema. Smaller doses of this medication are tolerated with few untoward effects, but she continues to get epistaxis following large injections of the medicine.

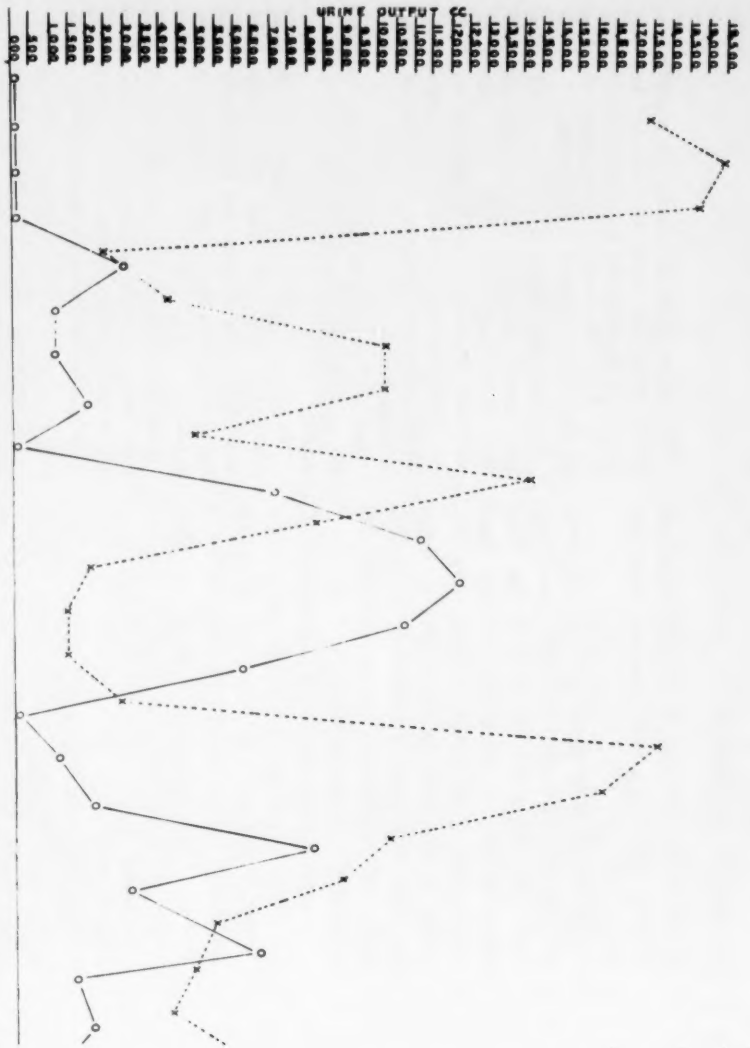
Method of Evaluation of Medication.—Each patient was advised to go without medicine until her thirst returned to the previous severity before medication was started. This was done, and the urine output was measured and averaged on an hourly output basis over an eight-hour period.

After this base was determined, the patient was advised to take the lozenges and place them under the tongue and record any sensations obtained and also to record the time of each voiding and the amount. This was carried out, and full cooperation was obtained. The patient was advised to try to keep herself as comfortable as she had been under other medication.

The urine output per hour on an eight-hour basis was recorded, along with the medication and how the medication was taken.

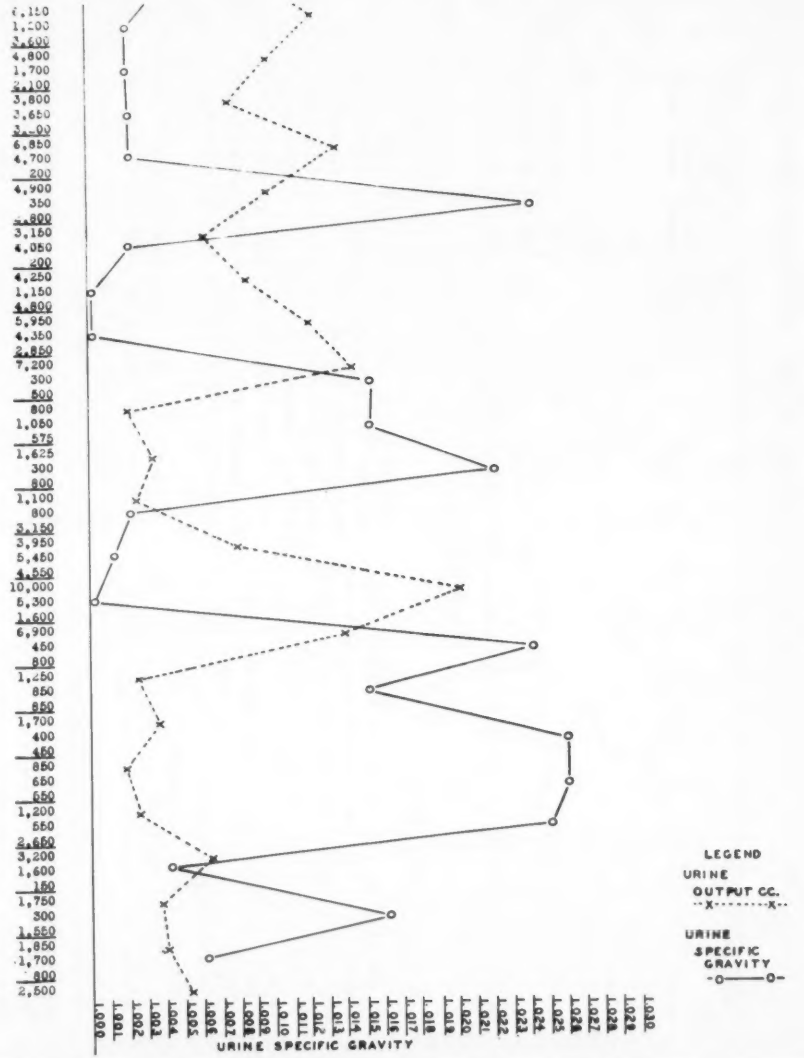
TABLE 10.—*Summary of Treatment in Diabetes Insipidus, Pituitary Type, Secondary, Case 40*

Day	Symptoms	Urine NaCl in 24 Hr., Gm.	Treatment	Urine Specific Gravity	Urine Output, Cc. 12 A. M.-12 P. M. 12 P. M.-12 A. M. 24-Hr. Total
1.	Excessive thirst and nervousness	....	None	1.000	9,050 8,400 17,450
2.	Excessive thirst and nervousness	....	None	1.000	9,750 9,600 19,350
3.	Excessive thirst and nervousness	12.22 *	None	1.001	9,100 9,750 18,850
4.	Thirst ceased 1½ hr. after injection; cramps at 10 p.m.; nausea and vomiting at 12 a.m.; menses ceased after 2 hr.	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.000	1,350 1,050 2,400
5.	Continued to have cramps in abdomen; no thirst	....	None	1.006	1,500 2,550 4,050
6.	First thirst 43 hr. after injection; noted dryness in nose and mouth; dyspnea	....	None	1.002	3,050 7,000 10,050
7.	Dyspnea, thirst, nervous, irritable, felt warm; thirst ceased 2½ hr. after injection; cramps, nausea, no vomiting	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.002	9,050 950 10,000
8.	Increased appetite; thirst returned 30 hr. after injection	....	None	1.004	1,000 3,750 4,750
9.	Returned to usual thirst	....	None	1.000	5,400 9,600 15,000
10.	Thirst ceased 2 hr. after injection; nausea, no vomiting	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1,014	6,700 1,600 8,300
11.	Few cramps, no nausea, eyes felt swollen	17.0	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.022	1,550 1,700 600
12.	Dyspnea; eyes felt swollen	12.9	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.024	950 1,450
13.	No symptoms	10.5	Vasopressin tannate, 5 pressor units plus placebo i.m., at 12 p.m.	1.021	900 450 1,250
14.	Urine output increased 2 hr. before onset of thirst	....	Placebo i.m.	1.012	7,5 2,000 9,5
15.	Normal thirst return	....	Placebo i.m.	1.000	7,875 9,450 17,325
16.	Normal thirst present	....	Placebo i.m.	1.002	9,[illegible]5 6,675 15,700
17.	Thirst ceased 3 hr. after injection; headache and severe cough	....	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.004	7,000 3,200 10,200
18.	Cough after medication	....	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.016	1,910 2,700 4,610
19.	Cough after medication	....	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.006	1,700 2,700 4,400
20.	Diarrhea, pruritus under chin, dyspnea; T., 98.6 F; P., 84; B.P., 130/80	5.82	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.013	1,910 3,000 4,910
21.	Headache, sensation of fever, pruritus under chin, dyspnea	4.85	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.003	3,[illegible]00 950 4,150
22.	Sneezing and vomiting following coughing after medication	3.43	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.004	1,100 2,050



23.	Sneezing and vomiting following coughing after medication; thirst noted	....	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.002
24.	Above symptoms aggravated	....	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.002
25.	Aggravated symptoms; thirst returned while taking medicine	....	Posterior pituitary powder, U.S.P., 40 mg. q.i.d.	1.002
26.	Macular red rash over whole body 4 hr. after medication; pruritus, cough	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.002
27.	Cough continued, rash faded	....	None	1.024
28.	Generalized aching, rash disappeared, cough continued	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.002
29.	Thirst started 2 hr. after urine output increased	....	None	1.000
30.	Thirst ceased 2 hr. after medication	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.000
31.	No thirst	....	None	1.015
32.	No thirst	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.015
33.	No thirst and no cough	....	None	1.022
34.	Increased urine output started 3 hr. before thirst; no cough	....	None	1.002
35.	Posterior pituitary tried again; severe cough resulted in vomiting; medication discontinued because of symptoms	....	Posterior pituitary powder, U.S.P., 40 mg. once	1.001
36.	Thirst ceased 2 hr. after injection	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.000
37.	No thirst	....	None	1.024
38.	Menses started	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.015
39.	No thirst	....	None	1.026
40.	No thirst	10.5	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.026
41.	Thirst 31 hr. after injection	....	None	1.025
42.	Severe thirst in a.m.	....	Vasopressin tannate, 5 pressor units i.m., injected at 12 p.m.	1.004
43.	Menses ceased, normal	....	None	1.016
44.	Increased urine output noted 13 hr. before onset of thirst	....	Vasopressin tannate, 5 pressor units i.m.	1.006

* Average of the first three days without treatment.



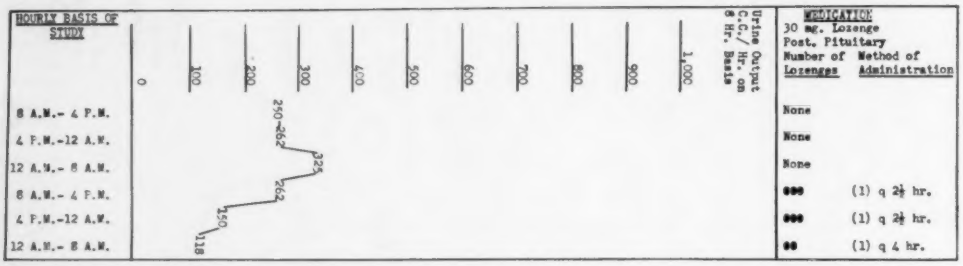


Figure 12 (Case 44).

Results of Medication

Case 44 (Fig. 12).—After a base urine output of about 262 cc. per hour was obtained, the patient took 1 lozenge about every two and one-half hours for the first 16 hours and then 1 lozenge every 4 hours. The urine output diminished rapidly down to 118 cc. per hour over the last eight-hour period.

The patient complained of the sweet taste in the mouth, and although the thirst was immediately relieved she still had the sensation of a full bladder. She stated that the result was rapid but that she preferred the vasopressin tannate in oil, although she did still get some reaction from the medication and disliked the necessity of hypodermic injections. She thought the medication had a definite place in the treatment of the disease. She could not take the posterior pituitary powder as snuff because of nasal irritation, and, as in all cases, the action of the vasopressin tannate stopped rapidly, often at inconvenient times, and to have a few lozenges handy relieved her of inconvenience.

Case 42 (Fig. 13).—This patient is well controlled on posterior pituitary powder, as demonstrated in her study. Her base output of urine was about 424 cc. per hour on an eight-hour basis when she was not taking the medication. Her study demonstrates well the desirable effect of the medication. The urine output was well controlled when she took 1 lozenge every four hours. The output went up when she discontinued the medication. This patient was very happy with the treatment and desired to continue under this type of management.

Case 40 (Fig. 14).—This patient was well controlled on small amounts of vasopressin tannate in oil. Without medication she reached a peak of 563 cc. per hour urine output over an eight-hour period. She did considerable experimenting with different routines of treatment. Her response was better when taking 1 lozenge every four hours. The effect was not as good when she took 2 lozenges every four hours. This action could not be explained. The last 16 hours, taking 1 lozenge every 3 hours produced good results. This patient, however, had the same complaints as in Case 44 in that she did not like the sweet taste it left in

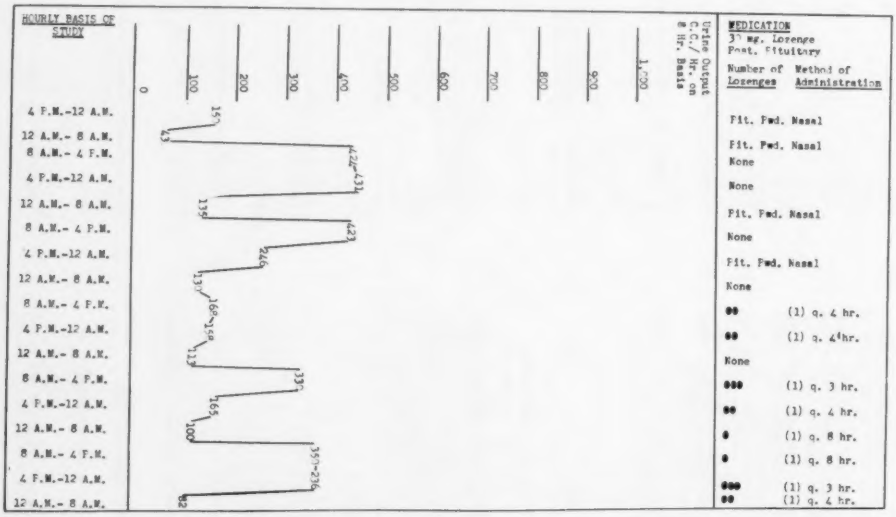


Figure 13 (Case 42).

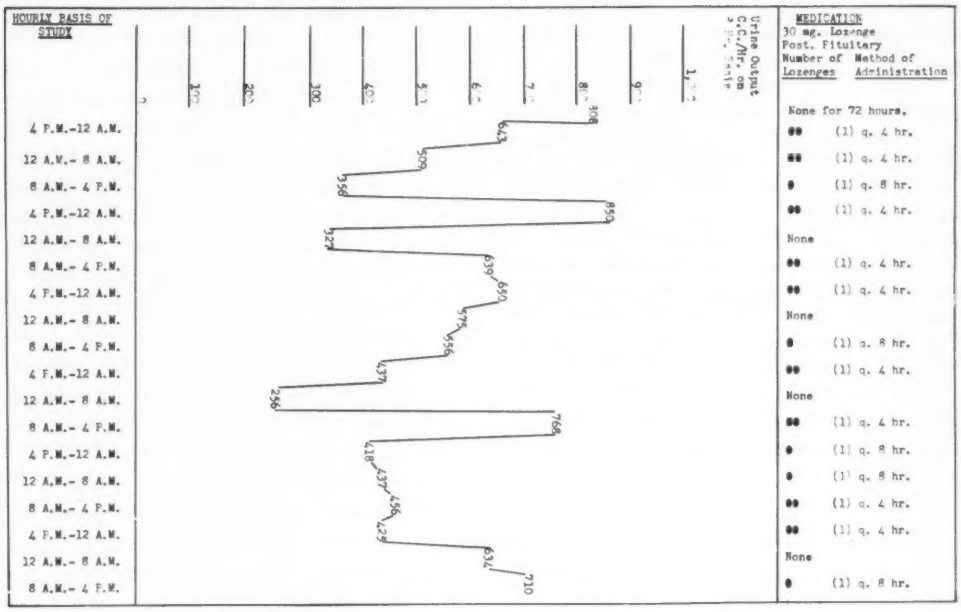


Figure 14 (Case 40).

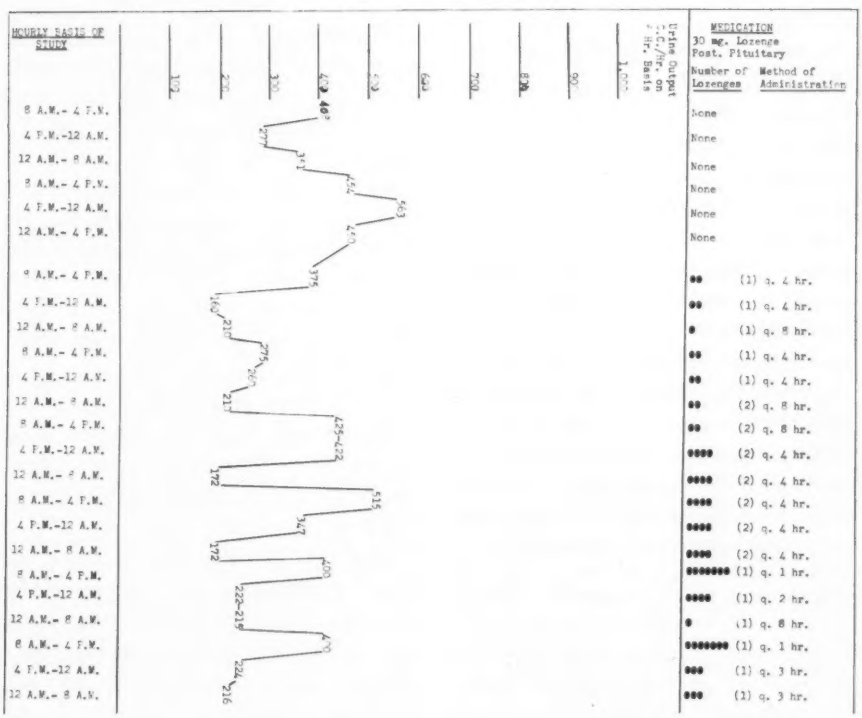


Figure 15 (Case 45).

the mouth. She liked the immediate effect of relief of thirst in the mouth but she, too, complained of the sensation of a full bladder.

Case 45 (Fig. 15).—This patient has a base urine output without treatment of 808 cc. per hour on an eight-hour basis. She took the lozenges in the routine of 1 every four hours. They gave her a desirable night's rest without medication. They gave her a convenient method of stopping the thirst when the vasopressin tannate would wear off. They were effective in decreasing the urine output, as noted in the study, and withholding the medicine did let the increased urine output return. The patient objected greatly to the sweet taste left in her mouth, and she thought this so objectionable that she preferred to go back to the treatment of vasopressin tannate in oil. She did desire some of the lozenges to keep handy for convenience, as she is unable to take the posterior pituitary as snuff.

Summary of Various Methods of Treatment

The disadvantages and objectionable factors along with advantages in the present method of treating diabetes insipidus are as follows:

1. Posterior pituitary requires repeated injections.
2. Vasopressin tannate in oil is costly and difficult to handle.
3. Posterior pituitary powder as snuff is often irritating but is economical.
4. Lozenges of posterior pituitary, 30 mg. each, are effective when taken every four hours.
5. Lozenges have the undesirable effect of causing a sweet taste in the mouth which is objectionable.
6. Lozenges are convenient in their use and can be used to advantage in conjunction with other methods of treatment.
7. The lozenges are convenient to use in the diagnosis of the pituitary type of diabetes insipidus, as they give immediate and definite relief of symptoms.

Recommendations as to Improving Methods of Treatment

1. Vasopressin tannate in oil should be put up in 10 cc. rubber-stoppered bottles. The advantages are that many patients do not need one whole cubic centimeter at one dose. In fact, the majority do not require 1 cc. These patients often save the residual of 1 cc. ampule for the next treatment. This, of course, is inconvenient. The mixing of the ampule is difficult and time-consuming. This could be eliminated by placing the well-mixed bottle in the refrigerator and bringing about a solidification before the active principles settled out. The next time it was used it could be warmed and the mixing would not take so much time. Proper mixing is important to get the full benefit of the drug. More uniformity could be obtained, thus necessitating no change in dose, which they all experience at present.
2. Posterior pituitary powder could be supplied in inhalators, such as are used at present in administering penicillin powder.

Observations Concerning the Extrapituitary, Hereditary Type of Diabetes Insipidus

The history of diabetes insipidus reads like a comedy of experimental errors, and it is hoped these observations will help to clarify rather than further complicate an already confusing picture.

In this study it has been demonstrated that there is an extrapituitary, hereditary type of diabetes insipidus. This is exemplified in Families 1 and 2. This section of the study concerns the site of the lesion. Although no definite site was determined, some interesting observations were made.

The absence of a method of treating the extrapituitary type of diabetes insipidus demonstrates clearly that factors other than the deficiency or absence of the antidiuretic factor are involved.

The lack of detailed postmortem studies have led some to assume there is an hereditary abnormality in the structure of the kidney. It has been demonstrated in this study that the kidney is anatomically normal, with a normal relationship between the various anatomical parts of the kidney tubules.

TABLE 11.—*Urine Findings in the Test for Antidiuretic Factor*

Urine Specimen	Sp. Gr.	Reaction	Albumin	Sugar	Sodium Chloride,* Mg./100 Cc.
1. Extrapituitary type					
(a) Before treatment	1.005	Alk.	Negative	Negative	17.5
(b) After treatment	1.004	Acid	Negative	Negative	13.3
2. Pituitary type					
(a) Before treatment	1.003	Neut.	Negative	Negative	122.8
(b) After treatment	1.024	Acid	Negative	Negative	731.2

* By dialysis all the sodium chloride was removed except in the pituitary type following treatment. This was 17 mg. per 100 cc., and the amount injected in the test was 0.17 mg., which would have a negligible effect.

The fate of the antidiuretic factor when supplied to the patient with the extrapituitary type is one important factor in determining the reason the patient does not respond with the usual marked, rapid diminution of thirst and urine output, as found in the pituitary type.

EXCRETION OF THE ANTIDIURETIC FACTOR IN THE URINE

The antidiuretic principle is excreted in the urine of the normal person. In order to determine whether or not patients with extrapituitary diabetes insipidus have the antidiuretic factor, samples of their urine (before and after treatment) were tested for this factor by injection of salt-free concentrated urine samples into hydrated rats. The rats' urine output was measured. These results were compared to like tests using distilled water and samples of urine from treated and untreated patients with the pituitary type of diabetes.

Urine samples were collected from patients with the two types of diabetes insipidus (extrapituitary and pituitary) after one week without treatment. The samples of urine following treatment were collected three hours after the injection of 1 cc. of vasopressin tannate in oil. The effect of the medication was noted 10 minutes after injection, and so an adequate amount of the antidiuretic factor was present. Other substances (sodium chloride and urea) were removed by dialysis through a cellophane membrane against running tap water. The urine samples became salt-free (except in one case), as noted in the summary of urine findings, Table 11. The samples of 200 cc. of urine of each type were concentrated, after dialysis, to 20 cc.

Various concentrations were tested. The one giving the most uniform results consisted of 1 cc. of the prepared urine in 14 cc. of distilled water. At this dilution all rats injected intraperitoneally with the urine from the pituitary type following treatment died with anuria.

At least four rats were used for each urine test, and the average urine output is shown in the graph demonstrating the results. It demonstrates several findings of interest (Fig. 16).

1. The urine of the patients with extrapituitary type diabetes insipidus, before treatment, has almost the same effect upon the urine output of the rat as does the urine from the untreated pituitary type of diabetes insipidus. The output is not as rapid as that following injection of distilled water. This suggests that in both types there is a deficiency of the antidiuretic factor.

2. The urine of patients with extrapituitary and pituitary types of diabetes insipidus, after treatment, has a marked effect on the urine output of the rat.

3. All rats treated with the urine from patients with the pituitary type, after treatment, died. A dilution of 0.1 cc. of the prepared urine was the smallest dose which consistently caused death. Smaller doses caused marked decrease in urinary output over a prolonged period.

4. The rats treated with the urine from patients with the extrapituitary type, after treatment, showed diminished output over a prolonged period. Two of the six rats died

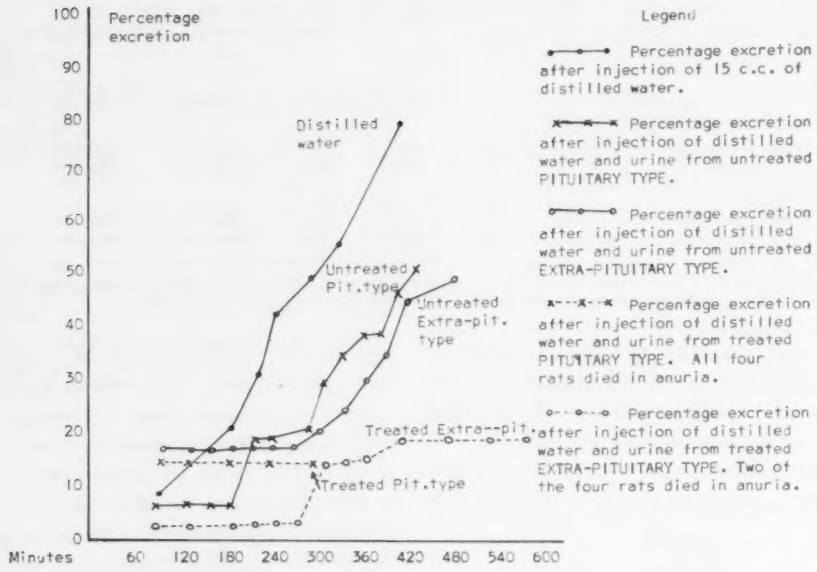

Percentage excretion
Legend
Percentage excretion after injection of 15 c.c. of distilled water.
Percentage excretion after injection of distilled water and urine from untreated PITUITARY TYPE.
Percentage excretion after injection of distilled water and urine from untreated EXTRA-PITUITARY TYPE.
Percentage excretion after injection of distilled water and urine from treated PITUITARY TYPE. All four rats died in anuria.
Percentage excretion after injection of distilled water and urine from treated EXTRA-PITUITARY TYPE. Two of the four rats died in anuria.
Distilled water
Untreated Pit.type
Untreated Extra-pit. type
Treated Extra-pit.
Treated Pit.type
Minutes

Figure 16.

with anuria. (The smaller effect can be accounted for by those with the extrapituitary type continuing to excrete large amounts of urine while those with the pituitary type after treatment, excreted concentrated urine.)

Conclusion.—1. Patients with the extrapituitary, hereditary type of diabetes insipidus and patients with the pituitary type of diabetes insipidus do not have the antidiuretic factor in the urine.

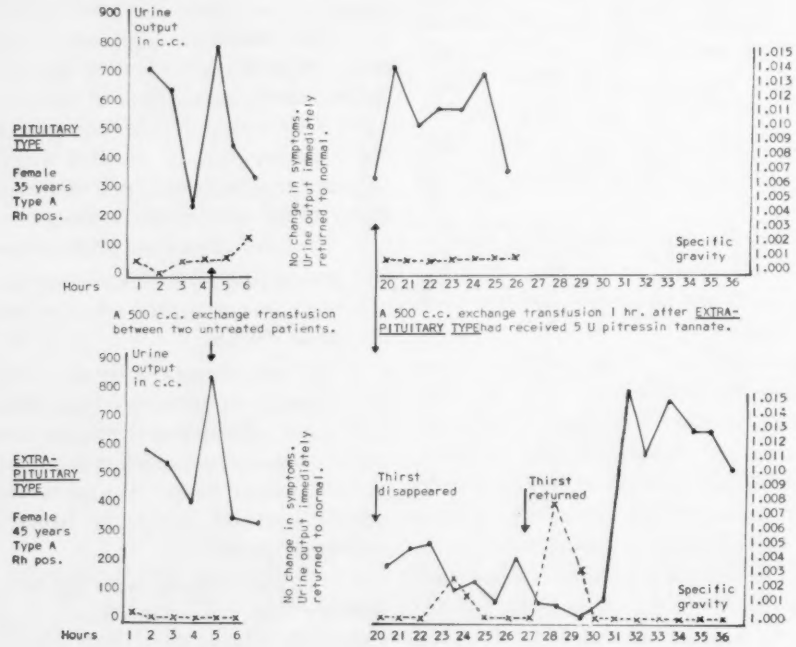

Urine output in c.c.
PITUITARY TYPE
Female 35 years Type A Rh pos.
Hours
No change in symptoms. Urine output immediately returned to normal.
Specific gravity
A 500 c.c. exchange transfusion between two untreated patients.
A 500 c.c. exchange transfusion 1 hr. after EXTRA-PITUITARY TYPE had received 5 U pitressin tannate.
EXTRA-PITUITARY TYPE
Female 45 years Type A Rh pos.
Thirst disappeared
Thirst returned

Figure 17.

2. When the antidiuretic factor is supplied, it is eliminated through the kidneys into the urine, as demonstrated by the antidiuretic response in the rat.

3. The patients with extrapituitary type of diabetes insipidus do not have the antidiuretic factor, and when it is supplied it is eliminated through the kidneys without effect upon the patient (but does have the effect upon the rat). Hence, it is assumed that, in addition to the patient's lacking the antidiuretic factor, the renal tubules of the patient do not respond when the factor is furnished.

Presence of the Antidiuretic Factor in the Blood

The response was determined to the antidiuretic factor by patients with extrapituitary type after they received vasopressin tannate in oil and a 500 cc. transfusion from an untreated patient with the pituitary type of diabetes insipidus.

The untreated patient with the pituitary type of diabetes insipidus is very responsive to small quantities of the antidiuretic factor. An exchange transfusion between untreated patients with the extrapituitary type and the pituitary type was carried out (Fig. 17), and no significant change in symptoms or urinary output was observed.

Twenty hours later, the patient with the extrapituitary type received 1 cc. of vasopressin tannate in oil, and one hour later another exchange transfusion was carried out with the pituitary type.

The result of this exchange transfusion and treatment was an immediate decrease in thirst and urinary output in the patient with the extrapituitary type. The specific gravity of the urine increased to 1.008 (Fig. 17). The patient with the pituitary type of diabetes insipidus noted no change in symptoms or urinary output until 36 hours after the exchange transfusion, and then symptoms sub-

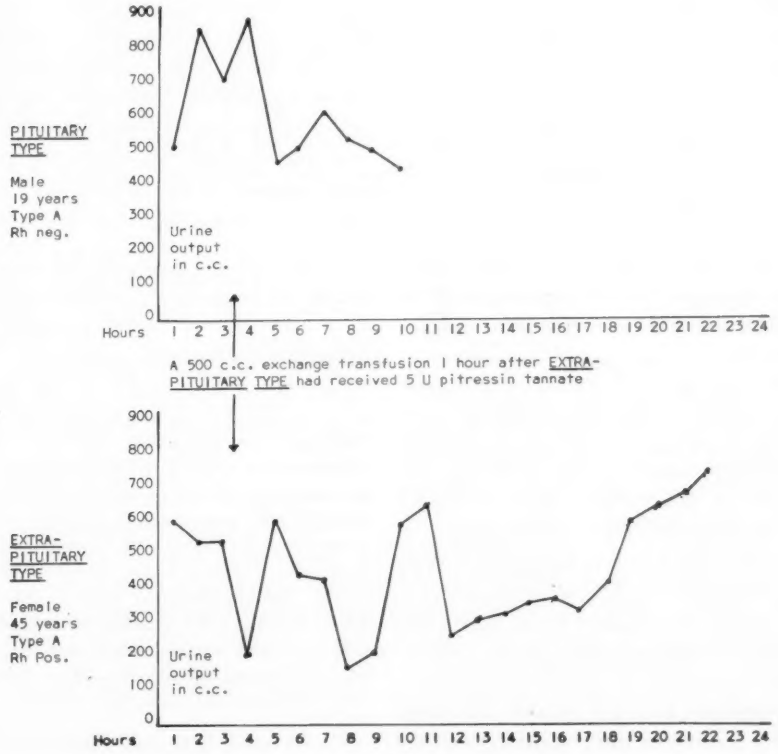


Figure 18.

sided and urinary output decreased for only a few hours.

The unusual response to the first two exchange transfusions led to another trial (Fig. 18). In this, only one exchange transfusion was done. The patient with the extrapituitary type received 1 cc. vasopressin tannate in oil, and one hour later an exchange transfusion showed that the patient with the pituitary type responded to the antidiuretic factor that had been injected into the extrapituitary type with a diminished thirst and urine output. The patient with extrapituitary type responded with diminished urine output for 19 hours.

A third transfusion was done, using 500 cc. of fresh citrated blood from a normal patient

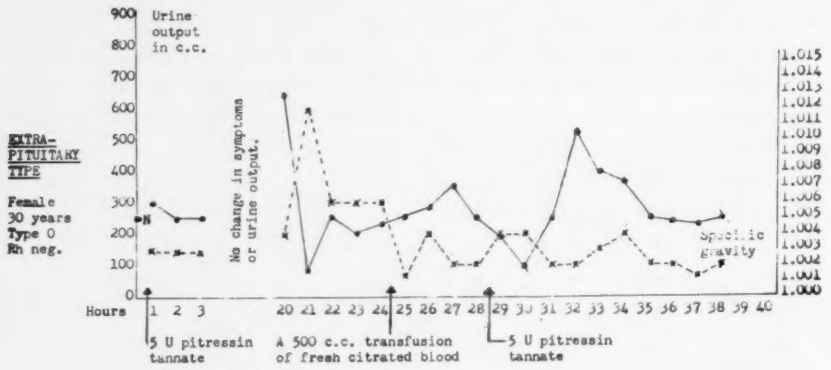

Urine output in c.c.
EXTRA-PITUITARY TYPE
Female 30 years Type O Rh neg.
No change in symptoms or urine output.
Specific gravity
Hours
5 U pitressin tannate
A 500 c.c. transfusion of fresh citrated blood
5 U pitressin tannate

Figure 19.

(Fig. 19). The patient with the extrapituitary type did not respond as well as when the blood from an untreated pituitary type was used.

1. Two patients with extrapituitary type diabetes insipidus, who had previously never responded to pituitary products, responded to vasopressin tannate in oil after they received 500 cc. transfusions from untreated patients with pituitary type diabetes insipidus.

2. One patient with extrapituitary type diabetes insipidus did not respond to vasopressin tannate in oil when a 500 cc. transfusion from a normal subject was given previously.

It is suggested by these results that there is a factor present in the pituitary type diabetes insipidus that when added to treatment of vasopressin tannate in oil makes it possible for the extrapituitary type to respond with diminished thirst and urine output and an increase in the specific gravity of the urine.

It is also suggested that there is a factor in the blood of the extrapituitary type that inhibits the function of the antidiuretic factor.

Other Methods Tried in Treatment of Extrapituitary Type

It has previously been reported that some women note symptoms of diabetes insipidus only when pregnant and others have noted a diminution of symptoms only when pregnant.

In this study there are more symptomatic extrapituitary type males than females.

These two observations led to a trial of the use of hormones in conjunction with the antidiuretic factor in the treatment of the extrapituitary type.

Case 33.—A man, 27 years of age, was treated with conjugated estrogenic substances (Premarin), 0.625 mg. three times daily, and 1 cc. vasopressin tannate in oil, with no decrease in urine output or in symptoms. He was treated with 10 mg. corticotropin and vasopressin, with no change being noted. He was treated with 20 mg. of testosterone propionate and vasopressin tannate and noted no change. He was treated with 500 cc. of blood from the blood bank and 1 cc. vasopressin tannate in oil, with a delayed response which was not as marked as when the patients received blood from patients with untreated pituitary type diabetes insipidus.

1. Female hormones, male hormones, and corticotropin had no beneficial effect in aiding

in the treatment of the extrapituitary type of diabetes insipidus.

Summary and Observations Concerning the Extrapituitary, Hereditary Type of Diabetes Insipidus

1. It has been demonstrated in this study that the kidney is anatomically normal, with a normal relationship between the various anatomical parts of the kidney tubules.

2. Patients with the extrapituitary, hereditary type of diabetes insipidus and patients with the pituitary type of diabetes insipidus do not have the antidiuretic factor in the urine.

3. When the antidiuretic factor is supplied it is eliminated through the kidneys into the urine, as demonstrated by the antidiuretic response in the rat.

4. The patients with extrapituitary type of diabetes insipidus do not have the antidiuretic factor, and when it is supplied it is eliminated through the kidneys without effect upon the patient (but does have the effect upon the rat). Hence, it is assumed that, in addition to the patient's lacking the antidiuretic factor, the renal tubules of the patient do not respond when the factor is furnished.

5. Two patients with extrapituitary type diabetes insipidus, who had previously never responded to pituitary products, responded to vasopressin tannate in oil after they received 500 cc. transfusions from untreated patients with pituitary type diabetes insipidus.

6. One patient with extrapituitary type diabetes insipidus did not respond to vasopressin tannate in oil when 500 cc. transfusion from a normal subject was given previously.

7. It is suggested by these results that there is a factor present in the pitiuitary type diabetes insipidus that when added to treatment of vasopressin tannate in oil makes it possible for the extrapituitary type to respond with diminished thirst and urine output and an increased specific gravity of the urine.

8. It is also suggested that there is a factor in the blood of the extrapituitary type that inhibits the function of the antidiuretic factor.

Summary

Clinically and etiologically diabetes insipidus is divided according to the following classification, the basis for which is presented in this study:

1. Pituitary type: There is pituitary deficiency, in which the symptoms are relieved by the administration of pituitary products
   (*a*) Primary (hereditary)
   (*b*) Secondary (postinfectious, neoplasms, etc.)
2. Extrapituitary type: The administration of pituitary products does not relieve the symptoms. It may may be hypothalamic; this type may be renal, with inadequate reabsorption; however, the kidney is histologically normal
   (*a*) Primary (hereditary)
   (*b*) Secondary (postinfectious, etc.)
3. Psychogenic polydipsia.

An historical review of the hereditary factor is presented.

The largest family tree of diabetes insipidus thus far studied is presented. This family demonstrates the hereditary factor in the extrapituitary type. The factor is followed through seven generations. In one case the factor appears after five generations of asymptomatic females. The inheritance factor is carried as a dominant factor with incomplete and even a low penetrance in the female. In this family there are 679 members, of whom 88 are involved with the disease. Twenty-two are asymptomatic female carriers. There are 55 males and 11 females with the disease.

A smaller second family is presented, showing the same inheritance factor.

Two family histories of the pituitary type of hereditary diabetes insipidus are presented to demonstrate the method in which this hereditary trait is transmitted.

This inheritance factor can be carried as a dominant characteristic with incomplete penetrance in the female.

An analysis of 22 cases of diabetes insipidus not known to be of hereditary type that respond to pituitary products and are not previously reported shows the etiological basis as follows: post-traumatic, 2; associated with Banti's disease, 1; encephalitis, 1; Hand-Schüller-Christian disease, 1; arachnoiditis, 1; subsequent to medication (vermifuge), 1; metastatic lesion from a carcinoma of the breast, 1; of unknown etiology, 14.

The morbid anatomy of the hereditary extrapituitary type shows a marked tendency to obesity. The skull films are consistently normal. There is megaureter and rapid elimination of the dye with a very large bladder in symptomatic cases.

A complete pathological summary is given on the first complete study made of the hereditary extrapituitary type. The kidneys and the pituitary are histologically normal.

Blood studies of the hereditary extrapituitary type show an inversion of the A/G ratio in the symptomatic members and tendency to inversion of the A/G ratio in the asymptomatic female carriers.

The age and life expectancy of the hereditary extrapituitary type show an increased early mortality rate, 8.5% dying before 3 years of age. Of those who had diabetes insipidus and reached 3 years of age, the average span of life was 46.6 years.

The symptoms of diabetes insipidus may be present at birth.

Various methods and complications of treatment are presented.

Cases reported are those pertinent to the present and future studies.

REPORT OF CASES

The cases reported are those most pertinent to the present study, and the other cases will be included in the reprints.

Cases 1 to 22: Symptomatic, Extrapituitary Type, Hereditary, Family 1

Case 1.—The patient was a 6-month-old girl (Family 1, Gen. VI, No. 18). Her father and two paternal uncles have diabetes insipidus. The infant was delivered without the aid of forceps. She was breast-fed, with interval feedings of water, until 1½ months of age, at which time she developed pyelitis with pyuria and vomiting. The child had not gained or developed well. Her weight was 7 lb. 14 oz. at 2½ months. Because of slow growth, the child was placed on a formula. Frequent vomiting was noted. The infant suddenly refused to take her feedings, "even water." On admission to the hospital her temperature was 99.4 F; pulse rate, 108; respiration rate, 20. The child did not appear acutely ill. The physical examination was essentially negative except for malnutrition.

Examination of the blood showed a red cell count of 3,350,000, with 66% hemoglobin. The white cell

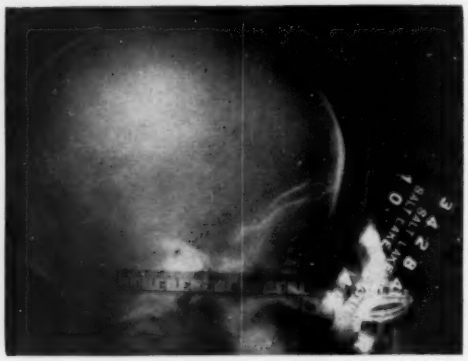


Fig. 20 (Case 1).—Skull film.

count was 9000. The differential white cell count showed 40% lymphocytes and 60% neutrophiles. Examination of the urine was done every three days. The specific gravity was not determined because of insufficient quantity. The urine showed an acid reaction, had a very faint trace of albumin, was negative for sugar, and showed several specimens to be loaded with pus cells and many to few bacteria, on microscopic examination. The culture gave a Staphylococcus, a few Gram-positive diplococci, and short-chained streptococci.

X-ray examination of the chest showed no evidence of a localized lesion in either lung and no persistent thymus.

Intravenous pyelography failed to produce visible pyelograms after the injection of iodopyracet (Diodrast) (Figs. 21 and 22). The area was somewhat obscured by flatus, in spite of efforts to clear the colon. Cystoscopy was done, and catheterization of the ureters was attempted with Butter-

Fig. 21 (Case 1).—Preliminary film.

field and Young infant cystoscopes. Although the orifices were well visualized, it was impossible to introduce ureteral catheters any distance beyond 1 cm. above the bladder. A second cystoscopy was done 3 days later, and a third was done 10 days later, with identical results.

The infant developed a temperature up to 103 F at times during 44 days of hospitalization. Many bacteria were found in the urine, and the urinary picture remained unchanged during the whole hospital stay, while she was being treated with adequate doses of sulfathiazole, methenamine, U. S. P. (Urotropin), and methenamine mandelate (Mandelamine). During this time, in addition to the regular formula, an average of 200 cc. of fluid was given subcutaneously daily. The child left the hospital, at the request of the grandmother, with a temperature of 103 F and markedly dehydrated. The grandmother gave the child 8 oz. of water on arrival at home and since has given water as desired. The child has been well since.

At 8 months, the infant weighed 13 lb. 4 oz. and was 26 in. long; the head was 16 in. in circumference; the shoulders, 16½ in. in circumference; the arms, 10 in. in length, and the legs, 11½ in.

At 10 months, the infant weighed 16 lb. 6 oz.; the head was 17 in. in circumference, and the length was 27¼ in.

At 19 months, the infant weighed 19 lb. and was 30¼ in. in length; the head was 18 in. in circumference; the chest, 20 in. in circumference; the hips, 21 in. in circumference. The infant developed its first teeth at 15 months and at 19 months had five teeth. The child walked at 15 months.

A normal sella turcica was noted on x-ray examination (Fig. 20).

Case 2.—A 6-year-old boy (Gen. V, No. 224) died after an operation. There was no diabetes insipidus in the immediate family. The mother and grandmother have been studied in detail. They were found to be asymptomatic female carriers of the disease.

The hospital record and the history as told by the parents are used as a basis for the following information:

The child had diabetes insipidus "all his life." A brother and sister are symptom-free. The patient drank 2 to 3 qt. of water each night and had enuresis. The past history revealed that the child had had rheumatic fever. He had had a tonsillectomy at 3 years of age.

The terminating illness started one year previously as an acute otitis media. The membrane ruptured spontaneously, and the ear had drained at intervals for one year. The terminating exacerbation of the illness started with epigastric pain, nausea, and vomiting at intervals for nine days' duration. He developed pain in the right hip and kept the right knee flexed.

On admission, he was acutely ill, poorly nourished, but well developed. His temperature was 102.2 F; pulse rate, 120, and respiration rate, 28. His head, eyes, and mouth were normal. The chest was clear. The heart was normal in size, and no murmurs were heard. The abdomen was tender throughout, markedly so in the right lower

Fig. 22 (Case 1).—Intravenous pyelogram 10 minutes after injection.

quadrant. Marked rebound tenderness was present. "There is a large fluctuant mass in the lower abdomen which is quite freely movable and reduces in size, sometimes almost disappearing." The right rectus muscle was somewhat rigid. The right leg and thigh were flexed and caused pain on extension. The skin was hot and dry.

X-ray of the chest revealed a flocculent mottling through both lungs of a type indicative of massive collapse. There was no evidence of fluid nor of a bone lesion in the hip.

Blood examination on admission showed WBC 22,000; BUN 15 mg. per 100 cc.; creatinine 1.7 mg. per 100 cc.

Urinalysis showed straw-colored urine with a specific gravity of 1.006, negative for albumin and sugar; the microscopic examination was negative.

The course of the disease was progressively downhill, with a septic type of temperature elevation to 105 F each day. The fluid intake was never more than 3000 cc. in 24 hours. An exploratory laparotomy was done, and a distended thin-walled atonic bladder found, which extended up to the umbilicus, especially on the right side. The appendix was normal. There was about 50 cc. of clear, colorless fluid in the abdominal cavity. All other abdominal viscera were apparently normal. The child developed congestion in the left chest and died three days later.

At autopsy, the diabetes insipidus was ignored and, unfortunately, no microscopic examination was done. The important gross findings show a thin cloudy fluid covering the surface of the brain. Sections of the brain from before backward showed some edema but no evidence of abscess or tumor. In portions of the petrous bone there was evidence of infection. There was no evidence of infection posterior to the eye. Both lungs were partially collapsed owing to bilateral effusion of about 750 cc. of brown-yellow fluid with large flakes of yellow-gray fibrin. Nodular areas about 3 cm. in diameter were noted. Cut sections gave the appearance of hemorrhagic infarcts or bronchial pneumonia. Some areas showed definite abscess formation in the center; remaining areas showed congestion. The heart was normal in size and not remarkable. The abdominal cavity contained free fluid, gray-yellow, with yellow-gray fibrin flakes. The liver was slightly enlarged and showed moderate congestion. The gall bladder, pancreas, stomach, appendix, and small intestine were normal. The spleen was 70% enlarged and firm on section. The kidneys were normal in size, and the capsule stripped with ease, leaving smooth surfaces, except for prominent fetal lobulations. The left renal pelvis was dilated moderately, and the ureter was dilated to 1.5 cm. The urinary bladder was thickened and trabeculated. On the posterior surface behind the trigone there were hemorrhagic areas, apparently from distended veins.

Case 3.—An 11-year-old obese male student (Gen. V, No. 147) was held back two years in school because of poor eyesight. The mother does not have the symptoms of diabetes insipidus. The child had mumps, varicella, pertussis, measles, and German measles, and he had a tonsillectomy at 5 years of age. At this time the mother noted the vomiting of food, but the child could retain considerable amounts of water. The mother had two brothers with diabetes insipidus and immediately recognized the condition. From 10 days of age the child was given all the water he desired. If water was withheld the symptoms of nausea, "sweet odor" to the breath (a great deal like that noted in measles), emotional instability, crying, childish action, and a choking appeared. If water was withheld for five hours, a temperature of up to 101 F was noted. The vision has been poor, with a marked myopia. The child's health was generally poor, and he did not gain well until 5 years of age. Obesity first developed at 8 years of age.

The patient described the following sequence of events on going without water: marked thirst, epigastric pain, nausea, dry mouth, thick tongue, and emotional instability.

Physical examination showed a mentally normal, obese boy, 58 in. in height, weight 118 lb. The genitalia and sexual development were normal. The thyroid was slightly enlarged. The heart measured 6 cm. to the left and 3 cm. to the right of the midsternal line at the apex. The rate and rhythm were normal. There was a systolic murmur at the apex. The intravenous pyelogram postinjection films (Fig. 5) show dilation of the pelvis, calices, and entire ureter (Grade III on a basis of I to IV). The cystogram showed a large bladder outline. This picture was indicative of a lower urinary tract obstructive lesion of undetermined nature but probably of long duration. The physical examination and blood examination have been summarized in preceding discussion, as has the urine examination. The results of treatment are summarized under treatment.

X-ray examination of the skull shows a normal sella turcica (Fig. 6).

Case 4.—A 23-year-old student was known to have had diabetes insipidus from infancy (Gen. IV, No. 87). One brother and one nephew have diabetes insipidus. The patient had pneumonia at the age of 13 years and had the usual childhood diseases. He developed a right inguinal hernia at 17 years of age. At present he is well developed and has a ruddy complexion with slightly cyanotic lips. Desquamation of the epithelium of the lips is present. The patient states that each afternoon

regardless of the amount of water consumption his lips feel hot and give the sensation of developing "fever blisters." The patient has a "sweet odor" to his breath when he goes without water and becomes thirsty.

The physical examination, blood and urine examinations, and treatment have been summarized in the preceding discussion.

The cystogram outlined fairly well and showed a bladder outline somewhat larger than normal but otherwise within normal limits.

CASE 5.—A 27-year-old man (Gen. V, No. 38) was discharged from the U. S. Army because of diabetes insipidus and an inguinal hernia.

The family history showed that three brothers had diabetes insipidus. The mother and maternal grandmother were symptom-free, but the maternal great-grandfather had diabetes insipidus. The patient married at 25 years of age. The first child, a daughter, born in February, 1943, had diabetes insipidus.

During childhood the patient had measles and chicken-pox. In 1943 he had mumps, at which time his weight dropped from 195 to 160 lb. He had a tonsillectomy at 2 years of age. A right inguinal hernioplasty was done in 1937 under local anesthesia. He did not use alcohol, tobacco, or any medication. The patient wore glasses for astigmatism. He noted a morning cough with production of thick mucoid material. The patient "started to drink water excessively before his mother was out of confinement." He had to drink every two to three hours day and night, usually taking 4 to 6 glasses (8 oz. each) of water at a time. When the patient went without water, he noted symptoms of headache, thick slime in the mouth, and a sensation of hunger in the epigastrium which could be satisfied only by water consumption.

The physical, blood, and urine examinations, and the treatment, have been summarized in the preceding discussion.

On intravenous pyelography the first postinjection film showed insufficient medium to delineate the pyelogram. There was, however, an outline of renal shadow on both sides suggesting a concentration of medium. In subsequent films, the dye was too little concentrated to make possible a definite diagnosis, although there was some suggestion of a widening of the upper ureter on both sides. The cystogram in the last films showed an unusually large bladder.

CASE 6.—A 34-year-old salesman (Gen. V, No. 36) had two brothers and one niece with diabetes insipidus. The patient had measles, mumps, whooping cough, and chickenpox during his childhood. He used alcohol and tobacco moderately. He had a tonsillectomy at 19 years of age. He had osteomyelitis of the left mandible at 23 years of age and had had reactivation at 34 years. The patient stated that during his whole life he had drunk about 1 qt. of water each hour. The patient got up five to seven times each night to drink water. He stated that on going without water he got a burning sensation of the mouth and a swelling of the tongue. When the water supply was changed, it took about three days to get over an excessive thirst. He also noted excessive thirst after every meal. The patient liked a great deal of salt and seasoning in his food. He preferred ice water. After his marriage the patient rapidly gained 68 lb. He had taken thyroid and pituitary compounds and had lost some weight. He had voluntarily tried to diminish the water intake, but when it was measured it was found that he had not decreased the amount. He noted "bad breath" when thirsty.

Physical examination showed a slightly obese man; height 68 in., weight 190½ lb. His blood pressure was 120/70; pulse rate, 96, and temperature, 98.6 F. No physical abnormalities were found.

The blood examination showed RBC 4,080,000; hemoglobin 84%, and WBC 9800. The differential white cell count showed 68% neutrophiles, 31% lymphocytes, and 1% monocytes. The blood urea nitrogen was 14 mg. per 100 cc.; uric acid, 4 mg. per 100 cc.; calcium, 12 mg. per 100 cc., and the serological test for syphilis was negative. The blood phosphorus was 3.5 mg. per 100 cc.; cholesterol, 178.7 mg. per 100 cc., and blood chlorides, 245 mg. per 100 cc.

The total protein and the albumin-globulin ratio have been summarized in the preceding tabulation on blood studies.

The urine examination has been summarized in preceding tabulation on urine studies. The average output at each micturition in this case was 834 cc. per hour.

CASE 7.—A 40-year-old baker (Gen. V, No. 34) had two brothers and one niece with diabetes insipidus. As a child he had chickenpox, measles, and mumps. A tonsillectomy was done at 12 years of age. At 36 years of age, the patient developed arthritis, involving the elbows, knees, ankles, and back. At this time he weighed 225 lb., and the increase in weight increased the arthritic symptoms. He had a hemorrhoidectomy at 39 years. At the time of this study, the patient complained of arthritis and obesity. He was taking 3 grains (180 mg.) of thyroid and the B. M. R. was + 1% after two months of treatment. Other complaints were polydipsia and polyuria.

The patient was born at home at seven and one-half months gestation. At his birth, the mother noted that the child had excessive thirst and drank considerable water, and she "detected diabetes insipidus immediately." The child would at times retain water but vomit all other liquids. On going

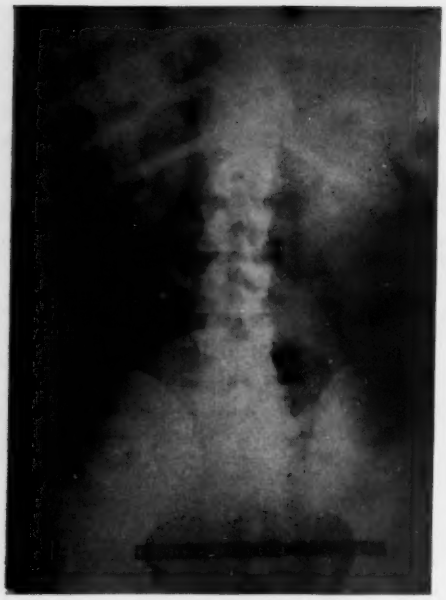


Fig. 23 (Case 7).—Intravenous pyelogram, 20 minutes after injection.

without water the patient noted symptoms after three or four hours. He first noted thickness of speech; a "thick slime" then formed on the lips and interior of the mouth. A change of water supply aggravated the symptoms. Well water was the cause of markedly increased symptoms. While traveling the patient coated his lips with petrolatum, but in spite of the precaution the cracking and dryness were severe. After a change of water supply the intake returned to normal in three days. Headache and marked nausea resulted later from going without water. After nausea became marked the patient vomited even water.

The essential physical findings have been tabulated in the preceding summary of physical findings.

The blood findings have been tabulated in the preceding table of blood studies.

The urinalysis, output, and treatment have been summarized in the preceding section on these subjects.

The 10-minute postinjection film of the intravenous pyelogram (Fig. 23) does not show the ureters clearly. The bladder is greatly enlarged.

The X-ray of the skull shows a normal sella turcica (Fig. 24).

Case 8.—A 42-year-old man (Gen. IV, No. 80), an attorney, had a mother with diabetes mellitus, one brother with diabetes insipidus, and one nephew, the child of a symptom-free mother, with diabetes insipidus. The patient had no children. As a child he had chickenpox, whooping cough, measles, and mumps, without complications. He had frequent epistaxis as a child. He had malaria in 1921-1922. A diagnosis of diabetes mellitus was made in 1932. The patient had had sinusitis, hypertension, chronic nephritis, albuminuria, diabetic retinitis, edema, and marked nervousness. At present the patient takes 25 units of regular insulin daily, along with theobromine and iron sulfate. He used tobacco moderately. He had had no surgical operations.

The patient stated that he had had diabetes insipidus during his whole life. He first noted a change in his health 12 years previous to the present examination, with increasing thirst and urination and increasing weight, from 155 to 175 lb. Excessive water drinking had gradually stopped, commencing seven to eight years previous to the present examination. The patient drank about 1½ gallons a day before the onset of the present illness.

The essential physical findings have been presented in the preceding summary on physical findings.

The blood chemistry findings have been tabulated in the preceding study of the blood findings.

The urine examination has been presented in the preceding summary. On various occasions the specific gravity of the urine was that of distilled water.

Because of ill health of the patient further studies were not advised. The patient died at the age of 44 of chronic nephritis.

Case 9.—A 57-year-old widow (Gen. III, No. 16) did housework for a living. The patient's father had diabetes insipidus. The history as to the children and presence or absence of diabetes insipidus was unreliable. She had had 16 pregnancies and had had five boys and eight girls. The menopause occurred at 49 years of age. For one year following she had menstrual bleeding and low back pain. She had measles, mumps, and chickenpox as a child. The past surgical history showed an ectopic pregnancy in 1923 and a vaginal hysterectomy in 1943. She lost her right eye in an accident

Fig. 24 (Case 7).—Skull film.

at 5 years of age. Her chief complaint had been dependent edema and dyspnea.

The onset of excessive water drinking was as early as the patient could remember. She drank about every two hours and never noted any discomfort or harmful effect. While working as a charwoman in a hotel she drank water in one room, voided in the next, and so on. The patient was hospitalized and, while unable to get up, drank the water from the hot water bottle in order to avoid divulging the fact that she had diabetes insipidus. The patient was sensitive about having the disease and later refused to cooperate with further studies.

Physical examination showed an obese woman with a blood pressure of 138/84. The respirations were 18. The right eye was blind; the left, normal. The thyroid was slightly enlarged. The heart rate was 84. A systolic murmur at the apex was noted. The heart measured 11 cm. to the left and 3 cm. to the right of the midsternal line in the sixth interspace. External and internal hemorrhoids were present.

The blood examination has been summarized in the preceding discussion under blood studies.

The times and amounts of each urination are tabulated below to show the volume of the bladder under normal conditions:

6 p. m.	1300 cc.	10 a. m.	1300 cc.
8 p. m.	1300 cc.	12 noon	1300 cc.
10 p. m.	1400 cc.	2 p. m.	1400 cc.
3 a. m.	1700 cc.	4 p. m.	1450 cc.
5 a. m.	1800 cc.	6 p. m.	1300 cc.
8 a. m.	1300 cc.		
			15,550 cc.

On intravenous pyelography, preliminary examination of the kidney showed it to be normal in position, size, and contour. No calculi were noted here or in the ureteral region. Good visualization was secured at 30 minutes. The right side showed moderate hydronephrosis with pyelitis and some ureteral diminution. The left was incomplete, but no definite pathology was noted. The 60-minute plate showed considerable diminution, but the dye is retained in the right kidney pelvis.

Conclusion: Hydronephrosis of the right kidney, cause not apparent.

CASE 10.—A 30-year-old woman (Gen. IV, No. 83) has had excessive thirst her "whole life." The family history revealed that her father had diabetes insipidus. Both of her children, her two sisters, and one brother were asymptomatic.

During childhood the patient had rheumatic fever and the common childhood diseases. The patient married at 21 years of age and had had two children. Her menstrual history was normal. She had not previously sought medical advice concerning the symptoms of diabetes insipidus.

Physical examination revealed a slender white woman, weighing 122 lb. and 63 in. tall. The systolic blood pressure was 120; diastolic, 76; pulse rate, 96; temperature, 98 F. An edentulous mouth was noted. The heart measured 6 cm. to the left and 3 cm. to the right of the midsternal line. There was a systolic murmur at the apex.

The blood cell count was normal. The blood sugar was 110 mg. per 100 cc. The total serum protein was 5.9 gm.; albumin, 3.24 gm.; globulin, 2.59 gm. (A/G ratio, 1.25). The serological test for syphilis was negative.

The urine was water-clear, with a specific gravity of 1.000, negative for albumin and sugar. The average output for 24 hours was approximately 14,000 cc. During the concentration test the patient was unable to go more than three hours without drinking water. The specific gravity of the concentration specimen was 1.000, and no albumin or sugar was present.

The basal metabolic rate had been +25%, +33%, and +38% on three different occasions. The patient showed some symptoms of hyperthyroidism.

On intravenous pyelography an insufficient amount of dye was concentrated to demonstrate the kidney. The bladder reached the maximal size in the 20-minute film and appeared larger than normal.

Free hydrochloric acid was present in the gastric analysis only after histamine was given. X-ray examination of the gastrointestinal tract was normal except for a very large stomach (Fig. 25).

Fig. 25 (Case 10).—Stomach film in extrapituitary type of diabetes insipidus.

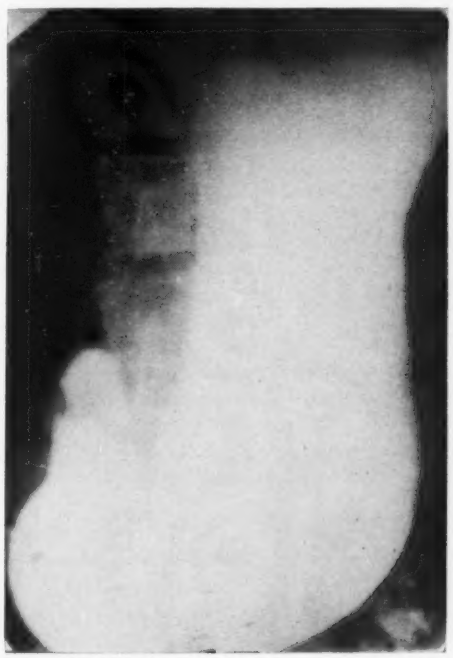


Fig. 26 (Case 10).—Skull film in extrapituitary type of diabetes insipidus.

The sella turcica was normal on x-ray examination (Fig. 26).

Case 15.—A 15-year-old boy (Gen. V, No. 205) was brought to the clinic for treatment by his mother.

The chief complaints were diabetes insipidus, incontinence, and enuresis of one year's duration. During the past year the patient had also had some personality changes.

The symptoms of diabetes insipidus were noted shortly after the child was born. During his early years he had had uncomplicated measles and chickenpox. At 9 years of age he developed encephalitis. He was unconscious for 16 days. Since the encephalitis he had been progressively more difficult to control. He quit school in the eighth grade, at which time it was recognized he was only doing sixth grade work. He would often walk 10 miles for no particular reason. He had recently had one experience with the police officers.

During the past year he had noted enuresis and incontinence. His abdomen was larger than previously.

Physical examination revealed a boy 66¾ in. in height and weighing 106 lb. His abdomen had the appearance of a six-month pregnancy, with enlargement extending from the pubis up to the umbilicus.

The systolic blood pressure was 108; diastolic, 80; pulse rate, 60; temperature, 98.6 F. The physical findings were otherwise normal.

The hemoglobin was 75%; RBC, 4,280,000; WBC, 8100. The serological test for syphilis was negative. The serum total protein was 6.03 gm.; albumin, 4.61 gm.; globulin, 1.0 gm. The albumin-globulin ratio was 5:1.

The urinalysis showed a specific gravity of 1.000 and acid reaction and was negative for albumin and sugar.

The patient voided and was immediately catheterized, 1560 cc. of urine being obtained. The distention of the abdomen immediately disappeared.

The skull film showed a normal sella turcica.

Intravenous pyelograms showed a markedly distended bladder, extending up to the umbilicus. Cystoscopic examination revealed no marked tightness of the sphincters. There were marked trabeculations of the bladder. Retrograde pyelograms (Fig. 27) revealed dilated, tortuous ureters with dilatation of the renal pelvis which decreased the amount of renal cortex.

After subsequent examination and with manual pressure, the patient was able to empty the bladder. In this manner the incontinence was controlled.

Pituitary products had no effect upon the urinary output, which was more than 12,000 cc. in 24 hours.

Case 19.—A 51-year-old white male auto dealer (Gen. IV, No. 39) had chief complaints of pain

Fig. 27 (Case 15).—Retrograde pyelogram in the extrapituitary type of diabetes insipidus.

in the right upper abdominal quadrant and generalized abdominal distress for years. The patient had one brother with the symptoms of diabetes insipidus and one sister without symptoms who had four sons with the symptoms of diabetes insipidus. His mother did not have the symptoms.

The present illness dates back years, when he first noted intolerance to fatty foods. He had had some severe right upper quadrant pain which required hypodermic injections for relief. The past year his symptoms had been more frequent and acute.

The patient had had an appendectomy at 21 years of age and a hemorrhoidectomy at 48 years. He had had diabetes insipidus all his life.

Physical examination revealed a white man, slightly obese, 65½ in. tall and weighing 161 lb. The systolic blood pressure was 110; diastolic, 70; pulse rate, 84; temperature, 97 F. The examination was otherwise negative, there being no tenderness over the gall-bladder area.

The EKG indicated right bundle branch block.

Blood examination showed RBC 5,050,000 hemoglobin, 83%; WBC, 9150. The sedimentation rate was 2.5 mm. in one hour. The serological test for syphilis was negative.

The phenolsulfonphthalein test showed 46% in one hour and 11% in two hours.

The fasting blood sugar was 200 mg. per 100 cc. The glucose-tolerance test gave the following results:

Time, Hr.	Blood Glucose, Mg./ 100 Cc.	Urine Glucose
½	200	Very faint trace
1	379	Negative
2	398	4+
3	298	4+

Preoperatively the diabetes mellitus was controlled by diet. A cholecystectomy was done, and postoperatively constant intravenous fluids were given for the first 24 hours, after which time oral fluids were given as desired.

CASES 23 TO 27: *Asymptomatic Female Carriers, Extrapituitary Type, Hereditary, Family 1*

CASE 23.—A 36-year-old obese housewife (Gen. IV, No. 83) has a mother who had diabetes mellitus and excreted an "average amount of urine." The patient's two brothers and one son have diabetes insipidus. The patient married at 18 years. Her first child, a girl, died at 17 months. The patient had one miscarriage at five months. She has three boys and one girl living. Her menarche was at 10 years of age; the periods are irregular; the interval is from two to six months, duration seven days, with no pain, excessive flow, and leucorrhea. She had had the usual childhood diseases, and she had influenza in 1918. She does not use medication, alcohol, or tobacco. She had a tonsillectomy at 13 years of age.

At present her chief complaint is painful joints. During the past four or five years she has noted stiffness and soreness of the joints. She has sudden extreme pain in the ankles at times. During her pregnancies she has had ankle swelling. She has some headache and dizziness. She has at times noted blurring of vision and hemianopia with marked dizziness. On suddenly arising she notes dizziness. She has some dyspnea on exertion.

Physical examination showed an obese white woman, 63½ in. tall; weight, 183½ lb.; systolic blood pressure, 128; diastolic, 76; pulse rate, 88; temperature, 98.8 F. No physical abnormalities were noted.

Physical examination is summarized in the preceding study on the physical findings.

Blood and urine findings are given in the preceding summary on these findings.

Treatment is presented in the summary of treatment.

On intravenous pyelography five minutes after injection, the dye appeared in fair concentration on both sides. The position of the kidney was normal. The left side showed a slight tendency toward congenital malrotation. The left ureter was not visualized throughout but appeared normal in the upper one-fourth. The right ureter presented an unusual angulation and tortuosity in the lower one-third. (This abnormality of the ureter is in keeping

Fig. 28 (Case 23).—Intravenous pyelogram five minutes after injection.

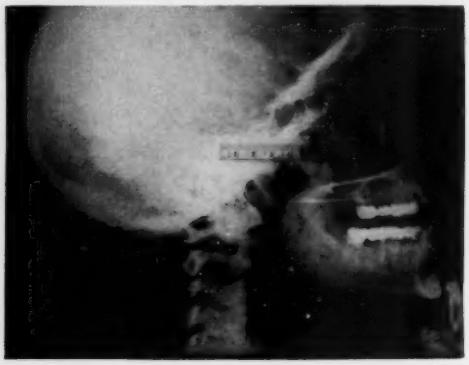
Fig. 29 (Case 23).—Intravenous pyelogram 20 minutes after injection.

with the type of distortion one sees following pregnancy.) The dye went through the kidneys rapidly and formed normal pyelograms (Figs. 28 and 29).

The x-ray of the skull showed a normal sella turcica (Fig. 30).

Case 24.—A 64-year-old obese housewife (Gen. IV, No. 23) had three sons and one granddaughter with diabetes insipidus. The patient married at 22 years of age and had six children. A record of a urine study when the patient was 44 years of age, at the time of her first admission to the hospital, showed a total output of 3500 cc. in 24 hours. The specific gravity was 1.020. It was later rechecked and found to be 1.012. It was negative for albumin and sugar.

Fig. 30 (Case 23).—Skull film.



The present physical findings are summarized in the preceding study of blood and urine findings.

The patient never drank water to excess. She had hypertension at 58 years. The systolic blood pressure was 174; diastolic, 112. She has had retinal hemorrhages. A glucose-tolerance test was normal. A loss of weight has apparently decreased the hypertension; however, kidney function is impaired.

Case 28.—A 3½-month-old infant was brought in by the parents because of frequent urination and vomiting. The child was a product of a difficult delivery, during which the cord was found to be around the neck. Childbirth was spontaneous, and birth weight was 7 lb. 2 oz. He was breast fed until the age of 2 weeks, and this was discontinued because of vomiting. At the age of 6 weeks a pyloromyotomy was done. This resulted in slight improvement. The child has been noted to have intermittent episodes of pyrexia which have not been accounted for. Various medications had been given, including intranasal vasopressin, without result. For about four weeks prior to admission, he had received cortisone, 25 mg. daily. This was discontinued just prior to admission to the hospital. He had used up to 18 diapers per day and had not gained weight well, maximum weight being 9 lb. 3 oz. When presented, he was found to be an acutely ill infant, almost in extremis. He had apparently recently regurgitated and aspirated some of his stomach contents. His skin was very hot and dry, and stomach contents were oozing from the nose and mouth.

Physical examination showed the temperature to be 107 F; the fontanel was open and slightly depressed. Funduscopic examination was negative. Ears were normal; pharynx was filled with stomach contents. Chest: rhonchi throughout lung fields. Abdomen: liver palpable, about 3 fingerbreadths below the costal margin; abdomen slightly distended; a well-healed scar was present. Extremities were symmetrical. Neurological study: all reflexes were noted to be hypoactive.

As the patient was first seen to be in extremis, he was immediately given emergency measures, which consisted of aspiration of the trachea and stomach, and intravenous fluids were begun. He was placed in oxygen and increased humidity. A lumbar puncture revealed normal spinal fluid which was clear; cell count was 32 cells, 60% lymphocytes. A tentative diagnosis of sepsis with dehydration was made. The patient was started on antibiotic therapy consisting of penicillin and streptomycin. Shortly after these measures were instituted, the patient was noted to have hypothermia, and he began some convulsive twitchings which lasted throughout the period of hospitalization. This child obviously presented a very difficult diagnostic problem. Many things were considered. There was a family tend-

ency towards diabetes insipidus, and this child represented a characteristic picture of the disease. He urinated 1500 cc. in one 24-hour period, during which time he also received about 1500 cc. of fluid. However, during no period of hospitalization was it felt that the child was adequately dehydrated. Blood chemistry examinations revealed a CO_2-combining power of 33 vol. %, with 117 mg. of chloride and 136.4 mg. of total base. At no time was the specific gravity of urine above 1.010. The child's course was one of progressive dehydration and apparently some neuropathy; he died on the third hospital day.

Hemoglobin was 12 gm.; WBC, 9000, subsequently 3000, with 25% polymorphonuclear cells, 25% stab cells, 30% lymphocytes, 7% monocytes; spinal fluid was negative; electrocardiogram was normal.

CASES 29 TO 33: *Hereditary and Extrapituitary Type, Family 2*

CASE 29.—A 51-year-old white man (Family 2, Gen. II, No. 4) had had an "eternal thirst" all his life.

The family history shows that the mother was symptom-free of diabetes insipidus, although one sister and some of her children had the disease. One sister does not have the symptoms, but some of her children do have the symptoms.

During childhood the patient had meningitis, rheumatism, measles, mumps, whooping cough, and chickenpox. The patient married at 26 years and has had six children. His chief complaint on admission was excessive thirst and pain in the lumbar region. He had had the excessive thirst as long as he could remember. He had never sought medical help, although he desired to be relieved of the symptoms.

Physical examination revealed a white man, weighing 174 lb. and 72½ in. tall. His systolic blood pressure was 120; diastolic, 80; pulse rate, 64; temperature, 98 F. No gross abnormalities were noted except that he was edentulous. The blood cell count was normal. The blood sugar was 96 mg. per 100 cc. The total serum protein was 4.54 gm.; albumin, 3.43 gm.; globulin, 1.07 gm., and A/G ratio 3.2. The serological test for syphilis was negative. The urine on admission was water-clear, and the specific gravity was 1.000. It was negative for albumin and sugar. The 24-hour output of urine was 20,500 cc. The patient was unable to go more than two hours without water and was unable to concentrate the urine above 1.000 in this period of time.

An intravenous pyelogram showed a rapid elimination of the dye, with a maximally enlarged cystogram 20 minutes after injection. The dye did not concentrate sufficiently to outline the kidneys and ureters.

The skull films were normal.

The patient was treated by injections of 1 cc. of vasopressin tannate in oil daily. After 14 days of treatment the 24-hour output was reduced to 15,600 cc. The patient continued to have nocturia and desired to discontinue the treatment. During treatment the urinalysis showed a specific gravity of 1.000.

The patient demonstrates well the unsuccessful treatment of the extrapituitary type of diabetes insipidus with pituitary products.

CASE 30.—A 45-year-old white woman (Family 2, Gen. II, No. 5) has six children, two of whom have diabetes insipidus. The patient's mother did not have the symptoms of diabetes insipidus. She has one brother with the symptoms.

As a child the patient had measles, scarlet fever, and whooping cough. As an adult she had smallpox. The patient married at 20 years of age and has had six children and no miscarriages. Her menstrual history has been normal. The patient has had no operation except the removal of all her teeth at 31 years of age.

This patient did not seek medical attention, but while we were studying other diseases in the family diabetes insipidus was noted to be present in three members. Her only complaints were obesity, low backache, and excessive thirst. She stated "it is not a thirst but the saliva seems to dry up." She can go eight hours without drinking liquids of any kind. She has always been obese, and she had severe headaches until 19 years of age, at which time they ceased. The low backache dates to an injury in 1934.

Physical examination revealed an obese edentulous white woman. The tonsils were present. The heart was 8 cm. to the left of the midsternal line and 3 cm. to the right. There were no abnormal sounds. The lungs were clear to auscultation and to percussion. The abdomen, extremities, and reflexes were normal. Pelvic examination was essentially negative. The patient weighed 201 lb. The systolic blood pressure was 140; diastolic, 84; pulse rate, 102, and temperature, 99 F.

The blood examination revealed 65% hemoglobin, with 4,240,000 RBC, 8900 WBC, and a normal white differential count. The blood sugar was 74 mg. per 100 cc.; the blood NaCl, 554 mg. per 100 cc. The total serum protein was 5.68 gm., with albumin 3.29 gm. and globulin 2.29 gm. The serological test for syphilis was negative.

The urinalysis revealed a water-clear urine with a specific gravity of 1.000, negative for albumin and sugar. The urine chlorides were 163.8 mg. per 100 cc. The average output was 8424 cc. in 24 hours. Treatment was instituted in the form of vasopressin tannate in oil (5 pressor units) intramuscularly every other day. The patient states that she was not as thirsty as previously but that the output of urine did not decrease appreciably.

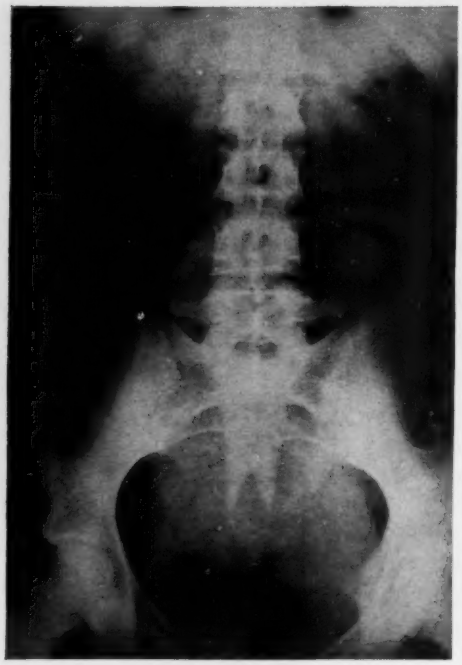


Figure 31 (Case 30).

Intravenous pyelograms showed a rapid excretion of the dye. The bladder reached the maximum size after 20 minutes and was about double the normal size. The dye did not concentrate sufficiently to show the kidneys and ureters. There was no change in the pyelogram after treatment (Fig. 31).

The skull film was normal (Fig. 32).

The treatment was not effective. The patient was satisfied with the results, as nocturia had ceased. Without treatment for two months she continued to have an output of 6200 cc., with a specific gravity of 1.000.

CASE 31.—A 16-year-old boy (Family 2, Gen. III, No. 30) had a brother and mother with diabetes insipidus. The patient had whooping cough at 2 years, chickenpox at 4 years, measles at 6 years, and mumps at 14 years. He had had numerous attacks of tonsillitis and had a tonsillectomy at 14 years.

Figure 32 (Case 30).

The patient's chief complaint was pain in the abdomen in the area of the umbilicus. He had some nausea and vomiting. A history of marked constipation was obtained. No definite tenderness in the abdomen was noted. The patient, in the course of the history, stated he had nocturia, and on further questioning a diagnosis of diabetes insipidus was made. The case led to a study of the family characteristic.

Physical examination showed the patient to be slightly obese, 67½ in. tall, weighing 136 lb. The systolic blood pressure was 100; diastolic, 72; pulse rate, 90, temperature, 100.2 F. The only abnormality was marked mottled appearance of the teeth. Operation for appendicitis was not recommended because of the few findings and the poor risk these patients have proved to be.

Blood examination showed a hemoglobin of 94%; RBC, 4,480,000; WBC, 11,200, with a normal differential count. Total protein was 6.72 gm.; albumin, 4.75 gm.; globulin, 1.31 gm., and A/G ratio, 3.6.

Urinalysis showed a water-clear urine with a specific gravity of 1.000, negative for albumin and sugar. The average 24-hour output was 18,504 cc. Urine chlorides were 117 mg. per 100 cc.

The intravenous pyelogram demonstrated rapid excretion of the dye, with kidneys and ureters not being well defined. The bladder was double the normal size.

The skull film was negative.

Treatment was started with vasopressin tannate in oil (5 pressor units) intramuscularly every other day, summarized under treatment. The patient thought his thirst had decreased under treatment. After having no medication for 60 days, the 24-hour output was 11,600 cc., with a specific gravity of 1.000 and negative for albumin and sugar, which is less than the average amount before treatment was started.

CASE 32.—An 8-year-old boy (Family 2, Gen. III, No. 32) had a mother and brother with diabetes insipidus. The boy did not seek treatment and had no complaints. At a few months of age the child had smallpox and measles, followed by pneumonia at 4 years and mumps at 6 years of age.

The patient started drinking excessive water at one month of age. At present he can not go longer than two hours day or night without a drink of water. On going without water the mouth becomes dry; then nausea and sometimes vomiting supervene. He states he prefers very cold water.

Physical examination revealed a slight boy, 52¾ in. tall, weighing 65 lb. His systolic blood pressure

was 110; diastolic, 68; pulse rate, 112; temperature, 100.4 F. The teeth were mottled. The heart extended to the left of the midsternal line 7½ cm. and to the right, 2 cm. There was a systolic murmur at the apex and at the base of the heart.

Blood examination showed 70% hemoglobin, 3,800,000 RBC, and 7500 WBC. The sedimentation rate was normal. The serological test for syphilis was negative. The fasting blood sugar was 96 mg. per 100 cc. The blood chlorides were 540 mg. per 100 cc. The total serum protein was 5.71 gm.; albumin, 4.33 gm., and globulin, 1.38 gm.; A/G ratio, 3.0.

Urinalysis revealed a water-clear urine with a specific gravity of 1.000 and was negative for albumin and sugar. The average output for 24 hours was 9504 cc.

This patient refused treatment because of its ineffectiveness in the other two members of the family treated.

CASE 33.—The patient is a 20-year-old white male missionary to the Indians in the southwest of the U. S. (Family 2, Gen. III, No. 35). The patient's mother did not have any symptoms, but his only brother has had diabetes insipidus all his life. The patient's past history was negative except for a tonsillectomy at the age of 10 years.

All the patient's life he had had the symptoms of diabetes insipidus.

On physical examination the patient was 65¾ in. tall and weighed 185 lb. The systolic blood pressure was 150; diastolic, 100; pulse rate, 104; temperature, 99.2 F. The only abnormality was the presence of severe dental caries.

The blood examination revealed a hemoglobin of 14.3 gm. and 92%; RBC, 5,000,000; WBC, 9400. The total protein was 6.0 gm.; albumin, 5.1 gm.; globulin, 0.9 gm., and the A/G ratio was 1:0.66.

The urinalysis showed a specific gravity of 1.002 and was negative for albumin and sugar.

CASES 34 TO 36: *Hereditary, Pituitary Type, Family 3*

CASE 34.—The patient (Family 3, Gen. II, No. 1) was a 47-year-old white housewife. Two of her four children have symptomatic diabetes insipidus. The patient had chickenpox at the age of 5 years, measles at 15 years, typhoid fever at 15 years, and pneumonia at 30 years. She had a tonsillectomy at 30 years and has had four children. Her menstrual history has been normal.

Her chief complaint on admission was excessive thirst, pain in the left lumbar region, and restlessness. Her history of diabetes insipidus dates back 17 years (age 30) when she first noted a "tired, worn-out condition." At the time she had a high fever for four days but noted no cough or pain in the chest. She was hospitalized at the time and remained there for 10 days. The attending physicians disagreed on the diagnosis but concluded she had "pneumonia." A few months after the patient returned home she noted a dryness of the mouth and excessive thirst. It seemed to be "more a condition of the mouth than a real thirst." The patient drinks water "every hour" at present.

At the delivery of her last child (in 1941) she received an injection which eliminated the thirst for several hours. She rested as she had not done for years. The patient inquired as to what the injection was and was told it was obstetrical pituitrin. She did not pursue the treatment.

Physical examination showed a well-developed and well-nourished white woman; weight was 113 lb.; height, 61½ in. Her systolic blood pressure was 122; diastolic, 70; temperature, 98 F.; pulse rate, 80. No abnormal findings were noted.

Blood examination revealed 71% hemoglobin, RBC, 3,520,000; WBC 10,180. The blood sugar was 96 mg., and blood chloride was 579 mg. per 100 cc. The total serum proteins were 5.2 gm.; albumin, 3.5 gm.; globulin, 2.3 gm., and A/G ratio, 1.52. The B. M. R. was +14%.

The urinalysis on admission showed a specific gravity of 1.008 and was negative for albumin and sugar. The average 24-hour output was 8100 cc. After a concentration test of five hours, the output diminished to 600 cc. during five hours, with a specific gravity of 1.012.

An intravenous pyelogram was made before treatment, which demonstrated a rapid elimination of the dye to form a rather large cystogram. The dye did not have sufficient concentration to outline the kidneys or the ureters. After treatment with posterior pituitary powder, U.S.P., there was a more marked outline of the bladder, which appeared smaller; the kidneys and ureters did not have sufficient dye to outline these organs.

The skull film (Fig. 33) showed a normal skull with a normal sella turcica.

The patient was started on posterior pituitary powder, U. S. P., 40 mg. q. i. d. The urinary output was 1100 cc. in the first 24 hours after treatment was started. The second 24-hour output decreased to only 525 cc., with a specific gravity of 1.014 and a trace of albumin. The patient was advised to regulate the dosage in order to obtain an output of between 1000 and 1500 cc. daily. She has had an excellent, uncomplicated response to the treatment.

CASE 39: *Asymptomatic Female Carrier of Hereditary Pituitary Type, Family 4*

CASE 39.—The patient (Family 4, Gen. III, No. 1) was a white female, whose father, one of two brothers, and only son had diabetes insipidus which responded to treatment with pituitary products.

Figure 33 (Case 34).

The patient married at 19 years of age and had three children. Her menstrual history was perfectly normal.

Her chief complaint on admission was pain in the right lower quadrant of the abdomen of one month's duration. She had noted some postmenstrual discharge for the past six months. Her periods were normal but for some dark red discharge following each period. The pain in the right lower quadrant came on with exertion and lasted about 15 minutes after resting.

Physical examination revealed an apparently healthy white woman, 63 in. in height and weighing 123½ lb. Her systolic blood pressure was 114; diastolic, 60; pulse rate, 60; temperature, 99 F. The examination was otherwise negative except for a mass 1½ to 2 in. in diameter in the right broad ligament that was definitely globular and seemed to be the ovary. The mass was tender and appeared to be inflammatory.

Blood examination showed hemoglobin, 82%; RBC, 4,150,000; WBC, 8900; sedimentation rate, 9 mm. in 60 minutes. The serological test for syphilis was negative. Examination of the vaginal smear was negative.

Cases 40-60: *Pituitary Type, Various Etiological Factors*

Case 40.—A 35-year-old white woman had never heard of diabetes insipidus and knew of no one with the disease.

The patient had scarlet fever at 3 years of age, pertussis and measles at 4 years, mumps at 7 years, chickenpox at 9 years, smallpox at 10 years, and typhoid fever at 13 years of age.

The menstrual history was regular until 1942. During the past six months it has become regular again. She has had three children, the last one in 1935.

She was in good health until 1942, at which time she had a "nervous breakdown" attributed to worrying about her children and husband. The husband was committed to the State Hospital for alcoholism. The patient became obese over a period of months and in May, 1942, developed a "terrible thirst" for cold water. No liquids but water satisfied the thirst. If she went a few hours without water she developed symptoms of nervousness, "feverishness," dry, thick sensation in the mouth, and the nose gave a very dry sensation. Owing to loss of sleep and fear of not being able to get a drink of water, she became extremely nervous.

Physical examination revealed an obese, nervous, apprehensive woman about 35 years of age. The teeth were in poor condition. Hypotonic musculature was noted throughout. Reflexes were hyperactive but equal. Pelvic examination revealed rectocele, cystocele, retroversion of the uterus, and hypertrophied clitoris.

On examination of the fundi, the discs were well outlined but a slight temporal pallor was present. Visual acuity in the right eye was 20/70, with slight astigmatism; that in the left eye, 20/40. Visual fields showed very slight contraction of the upper nasal quadrant. Convergence test showed divergence laterally of the right eye as objects were brought close.

The temperature and pulse were normal. The blood pressure was 126 systolic and 80 diastolic.

Blood examination revealed 75% hemoglobin; RBC, 4,020,000; WBC, 6200. The blood sugar was 85 mg. per 100 cc. The BUN was 17 mg. per 100 cc.

Fig. 34 (Case 40).—Skull film. Pituitary type of diabetes.

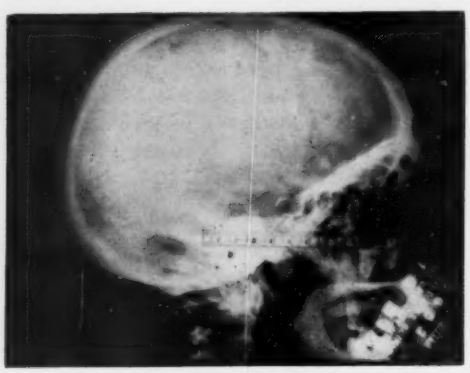


Fig. 35 (Case 40).—Preliminary film.

The total protein was 6.27 gm.; albumin, 4.14 gm., and globulin, 2.00 gm., with an A/G ratio of 2:1. The blood cholesterol was 195 mg. per 100 cc.; blood chlorides, 620 mg. per 100 cc. The glucose tolerance was normal. The phenolsulfonphthalein excretion while the patient was not being treated was 60% in two hours (690 cc. of urine), but while she was being treated with vasopressin tannate it was 15% in one and a half hours (75 cc. of urine). The B. M. R. was +14%.

Fig. 36 (Case 40).—Intravenous pyelogram 20 minutes after injection.

Fig. 37 (Case 40).—Intravenous pyelogram 45 minutes after injection.

Fig. 38 (Case 40).—After treatment. Preliminary film.

Fig. 39 (Case 40).—After treatment. Intravenous pyelogram five minutes after injection.

Roentgenograms of the bones of the skull showed no pathologic changes. The pituitary fossa was normal in size and appearance, and there was no evidence of an intrasellar or parasellar neoplasm (Fig. 34).

Fig. 40 (Case 40).—After treatment. Intravenous pyelogram 20 minutes after injection.

On intravenous pyelography, before treatment, there was insufficient concentration of dye to visualize the kidney, the kidney pelvis, or the ureters. The 45-minute film (Figs. 35 to 37) shows no definite pyelogram but a good concentration of the dye in the bladder, which was approximately five times normal size and elevated so that it was an abdominal organ. After treatment the dye showed good concentration in both kidneys after five minutes. There was excellent delineation of the pyelograms (Figs. 38 to 41). In five minutes after injection, there was only slight concentration of the dye in the bladder. The film 20 minutes after injection showed a fair concentration. The cystogram showed better concentration and great reduction in size.

Fig. 41 (Case 40).—After treatment. Intravenous pyelogram 45 minutes after injection.

The 45-minute postinjection film still showed good visualization of the kidneys and bladder. The bladder, irregular in outline, was slightly larger than expected. Treatment had greatly reduced the dilution of the media and the bladder capacity almost to normal.

The urine before treatment was water-clear, with specific gravity that of distilled water, and was negative for albumin and sugar.

The treatment of this patient has been summarized. It is noted that the specific gravity increases as the urine output decreases. The vasopressin tannate relieved the symptoms of thirst within two hours after injection. At times, it relieved the symptoms after a few minutes. The duration of the effect varied but was usually around 30 hours.

Increased urine output was noted by the patient before onset of symptoms of thirst and, owing to the variability of the duration of the effect of the drug, the increased output was used as an indicator of the necessity of more medication. The posterior pituitary powder by nasal insufflation was the method of choice by the patient; however, the untoward reaction of itching chin and severe cough, which would result in vomiting, made it impossible to continue this type of treatment. The method was tried a second time, but it produced severe coughing, the paroxysms of which lasted 20 minutes. The coughing made this type of medication undesirable in this case. The chloride output before treatment and during treatment with vasopressin tannate were nearly equal, while with the nasal posterior pituitary powder it was approximately half the usual amount. The importance of and reason for this finding were not further studied.

CASE 41.—A 40-year-old man, slow in speech, motion, and response to questions, having marked hypochondriacal tendencies, complained of pain in the chest of 25 years' duration and pain in the left leg and foot for the previous 3½ years. He had numerous other complaints, for which he had many explanations. He stated he "drinks a glass of water every twenty minutes and urinates about every half hour." The drinking of cold water relieved the symptoms in his chest and generally made him feel better. He also complained of nocturia.

His past history revealed he had the usual childhood diseases of measles, mumps, and pertussis. At the age of 7 years he came to the U. S. from Canada. In 1918, at the age of 13, he had epidemic influenza and was confined to bed with a high fever for two weeks. He went through the elementary school and the first year of high school without being retarded but during the first year of high school he developed slowness of speech and mentality. He quit school the following year at the age of 19. Two years after the slowness of speech started, the patient began the "drinking habit," and this habit was noted to be marked at the age of 28 years. He married at 27 years, had two children, and was divorced after 10 years of married life. Up to the present time he does fairly good oil painting. There is an obvious mental defect at present. The family stated that the patient had a normal childhood, with an undiagnosed fever at 13 years of age. There was a gradual onset of mental and personality changes five years later, with increasing symptoms of slowness of gait, of speech, and in the answering of questions. The excessive water drinking started after the onset of the foregoing symptoms. He is well oriented as to time and place and does simple calculations and is well informed on current events. The history is compatible with chronic encephalitis, which has previously been shown to be a frequent cause of diabetes insipidus. The family history was essentially negative.

Physical examination revealed a white man 67½ in. tall, weighing 158 lb. His pulse was 116; systolic blood pressure, 148, and diastolic, 108. The skin had brownish areas of pigmentation over the shoulders, back, and arms, and there was marked axillary perspiration. Dull facial expression was noted. Heart examination was normal but for a systolic pulmonic murmur. His tendon reflexes were hyperactive but equal. There was no palpable dorsalis pedis pulsation, and the lower extremities were slightly cyanotic.

Extraocular movements of the eyes were normal; pupils were round and regular and reacted to light and in accommodation. Fundi showed silver-wire vessels. Visual fields were normal.

Neurological examination showed his signs and symptoms to be hemiplegic in character and to involve the left side of the body. The difficulty with the left leg is obvious, and his left upper extremity is rigid and motionless as he walks. His gait is very characteristic; he stoops forward and trots in Japanese fashion. His tremor is bilateral but moderate. His facies is dull and somewhat masked. His cerebration is dull and slow. The reflexes are all bilaterally exaggerated, but no pathological reflexes were noted. The cremasteric and abdominal reflexes were absent. It was concluded from the neurological examination that the patient had pathology in the extrapyramidal system and that such a picture is compatible with that following encephalitis.

Blood examination revealed 91% hemoglobin; RBC 4,800,000 and WBC, 11,800. Differential white cell count revealed polymorphonuclear cells, 71%; lymphocytes, 26%; monocytes, 3%. Sedimentation rate was 3 mm. in an hour, and serologic tests were negative. Total protein was 6.72 gm.; albumin, 3.71 gm.; globulin, 2.58 gm.; fibrogen, 0.43 gm., and A/G ratio, 1.51. Blood sugar was 127 mg. per 100 cc.; plasma chlorides, 544 mg. per 100 cc.; blood urea nitrogen, 33.2 mg. per 100 cc.

Phenolsulfonphthalein test revealed 45.5% dye return in one and one-half hours in a total of 580 cc. of urine. X-ray of the chest was normal. B. M. R. was +6%. EKG showed a tendency to right axis deviation and was otherwise normal.

The intravenous pyelogram film five minutes after injection showed visualization of a part of the calyces of the right kidney only. The dye did not appear in sufficient concentration in the left kidney. There was a fair accumulation of dye in the bladder. Forty-five minutes after injection a slight amount was visualized over each kidney area. A good accumulation of dye appeared in the bladder. The resultant cystogram showed that the bladder shadow was enlarged at least half of the size of the normal bladder. Fragmentary visualiza-

Figure 42 (Case 41).

tion of the pyelograms was undoubtedly on the basis of dilute, rapid excretion.

X-ray of the skull showed normal sella turcica (Fig. 42).

Urine concentration test revealed that after 23 hours with no fluids the urine was straw-colored, with specific gravity 1.011 and acid reaction; it was negative for albumin and sugar, and microscopic examination was negative.

Total urine output was measured for each 24 hours, as tabulated below: Medication was tried with untoward symptoms.

	Day 1	Day 2	Day 3	Day 4
Urine output in 24 hr., cc.	12,000	17,025	16,925	17,325
Sp. Gr.	1.001	1.000	1.000	1.000
Total NaCl, gm.	16.15	.....	12.75	.....
Calcium	.....	.....	.....	.....
Treatment	None	None	None	None
Symptoms	None	None	None	None

Treatment was then started with intramuscular injection of 5 pressor units of vasopressin tannate in oil. The 24-hour urine output was 15,900 cc., with a specific gravity of 1.009 and a total NaCl output of 81.88 gm. The patient stated that he had consumed as much water as previously and did not have the urine output chart with him the next morning, and so the same medication was repeated at 10:30 a. m. The patient kept his chart until 4 p. m., and the total to this time was 2225 cc., which was a marked decrease in output. Five hours after the second injection, the patient appeared drowsy and responded poorly. Seven and one-half hours after the second injection he had a convulsion, with rigidity, "shaking," and incontinence followed by vomiting. He became semicomatose and would not respond to stimuli. Examination at this time revealed a blood pressure of 120/90. Pulse rate was 120. Pupils were small, regular, and reacted to light and in accommodation. Reflexes were equal but hyperactive. Sensorium was very clouded, and the patient vomited a brown watery fluid. Urinalysis revealed a specific gravity of 1.009 and was negative for albumin and sugar.

Blood examination revealed RBC 5,250,000; hemoglobin, 14.5 gm.; icteric index, 15, and sedimentation rate, 5 mm. in an hour. Blood urea nitrogen was 17.4 mg. per 100 cc.; plasma chlorides, 442.9 mg. per 100 cc.; blood sugar, 112 mg. per 100 cc., and blood calcium, 8.9 mg. per 100 cc.

Spinal lumbar puncture revealed a pressure of 200 mm. of water; dynamics showed 290 mm. on right carotid compression and 410 mm. on left carotid compression. Spinal fluid was clear; sugar, 88 mg. per 100 cc.; chlorides, 538 mg. per 100 cc.; serologic tests were negative, and gold curve was 1233210000.

The following day the patient remained semicomatose, and little change was noted. Oral and intravenous fluids were given. Urine output by catheterization was 5500 cc. for 24 hours.

On the following day, after 36 hours of semicomatose condition, the paitent suddenly became conscious; he could not remember anything that had transpired since a few hours after the second medication. The patient then began drinking his usual amounts of water. His blood pressure was 116/70. The intake was 8000 cc., and the output, 4000 cc. When the concentration test was repeated, the patient became irrational, and he returned suddenly to normal after drinking 500 cc. of water.

This case clearly indicates that patients should be warned to decrease intake of water while receiving medication, as water intoxication may result.

Case 42.—A 37-year-old housewife had chief complaints of diabetes insipidus, visual difficulties, and a tumor of the throat.

At 16 years of age the patient had had an appendectomy and one ovary was removed. The patient first noted the polyuria and polydipsia following this operation. The symptoms, however, were not severe. At 25 years she had a tonsillectomy, and at 26 years she had a hysterectomy and the remaining ovary was removed. It was following this operation that the symptoms became aggravated,, and treatment with obstetrical pituitrin was instituted, with relief of symptoms. The one treatment daily lasted her eight hours, and the remaining 16 hours she had the symptoms of polyuria and polydypsia.

Her past history revealed no other etiological factors, such as encephalitis, except that during the summer months during her first 12 years she experienced convulsions following episodes of diarrhea.

At 36 years, one year previous to present examination, she was hospitalized because of an unknown fever. During her hospitalization her urine output averaged about 11,000 cc. in each 24 hours.

Her family history revealed no evidence of diabetes insipidus. Her three sisters and two brothers were free of symptoms of the disease. Her parents, grandparents, and great-grandparents had no history of the disease.

Physical examination of the patient showed height 65½ in. and weight 125¾ lb. The systolic blood pressure was 130; diastolic, 86; pulse rate, 100; temperature, 98.6 F. There was a palpable spleen, and otherwise no abnormal findings were noted.

X-ray examination of the skull revealed a normal sella turcica.

Blood examination showed 72% hemoglobin; RBC, 3,500,000; WBC, 7300. The sedimentation rate was 14 mm. in 60 minutes. The field of vision was normal upon examination.

The patient was treated with posterior pituitary powder, U. S. P., and obtained excellent results, with no complication.

CASE 43.—The patient was first examined in 1922, at which time she was 6 years of age. She had four older brothers, all of whom were normal. The mother and father had no known abnormality. The mother was 39 years of age when the child was born.

The birth of the child was normal. The labor lasted 11 hours, and the baby was large (12 lb.). The baby was breast-fed for 18 months. She walked at 19 months, and her first tooth appeared at 10 months. The teeth appeared normally. She talked at 2 years, and her first 2 years appeared to be normal.

The patient had bronchitis at 7 months and chickenpox at 5 years. She had suffered no injury.

The chief complaint on admission was polyuria and underdevelopment. The child appeared to be about 4 years of age.

At about 3 years of age she began to drink large amounts of water and passed large amounts of urine. These symptoms became progressively worse. She noted no headaches. The diet was normal. Growth was slow after the first three years. Her weight had remained stationary at 34 lb. for the past three years. Her height was 37 in. The skin was dry and somewhat thicker than normal. The pulse rate was 104; temperature, 100 F.

The 24-hour urine output was 4025 cc. The specific gravity was 1.005, and the urine was negative for albumin and sugar. The blood sugar was 109 mg. per 100 cc.

The hemoglobin on admission was 21%, and after five transfusions the hemoglobin was 80%; RBC, 3,650,000; WBC, 18,000. The differential white cell count was normal. The serological test for syphilis was negative. The B. M. R. was +21%.

The patient was treated with 0.5 cc. of posterior pituitary, U. S. P., every two to three days and was maintained on the dosage.

At 29 years of age the patient was 56 in. tall and weighed 85 lb. The rest of the examination was negative except for a palpable spleen, which had been noted since childhood. At this time she was anemic and was given several transfusions. Her hemoglobin before transfusions was 40%, with RBC 2,050,000 and WBC 6300. The differential white cell count was normal. After the hemoglobin became 93%, the following studies were carried out: B. M. R., +9%; plasma cholesterol, 167 mg. per 100 cc.; intravenous hippuric acid test, 0.25 gm.; NPN, 21 mg. per 100 cc.; blood serum proteins, 5.95 gm.; albumin, 3.32 gm., and globulin, 2.63 gm.; rose Bengal test, 98% retention in eight minutes, 66% in 16 minutes (both this and the intravenous hippuric acid test showed marked liver damage). Red cell fragility was found to be normal. Complete bone studies were also found to be normal. Urine gonadtropin studies were within normal limits. Numerous x-rays were taken, including those of the skull, which were found to be normal. Plain films of the abdomen showed only splenomegaly. The chest film and the gastrointestinal series were normal. The visual peripheral fields were normal. Esophagoscopy showed no evidence of esophageal varices. A sternal marrow biopsy was taken which showed only hyperplasia of the bone marrow and no evidence of fat storage.

A splenectomy was carried out, and recovery was rapid.

At present, two years after the operation, the blood is normal and the patient is in good health except for the diabetes insipidus, which is controlled by vasopressin tannate in oil.

CASE 44.—This patient has no relative with diabetes insipidus and demonstrates the immediate reaction to pituitary products in the secondary types of diabetes insipidus, with an undesirable allergic response as another complication of the treatment.

The patient was a 52-year-old white graduate nurse with no family history of diabetes insipidus. She was born in Sweden. She had had the usual childhood diseases, with a tonsillectomy in 1913 and again in 1926. She married at 20 years of age and has had six children. Her menstrual history is normal. She went through the menopause at 50 years, without untoward symptoms.

Her chief complaint on admission was excessive thirst, pain in the left knee, emotional instability, and restlessness. Her history of diabetes insipidus dated back to three months before admission, at which time the patient developed a head cold. She had no sensation of fever. She noted increased sleepiness and stated that she "could fall asleep any time," but she attributed this symptom to her not being able to sleep more than two hours without getting up to drink water. At the time of the acute illness she noted "loads of mucus and froth in the mouth." As the symptoms of the cold subsided she gradually developed excessive thirst.

At the time of examination, the patient stated she drank from 45 to 50 glasses of water every 24 hours. She also complained of a burning in the epigastrium every three weeks. Before the onset of thirst, the

tongue gave the sensation of being "scalded." The patient had gained 4 lb. during the three months of illness. She became apprehensive and emotionally unstable.

Physical examination showed a slightly obese white woman; weight was 153 lb.; height, 62 in. Her systolic blood pressure was 120; diastolic, 78; temperature, 98.6 F; pulse rate, 78. The only abnormal findings noted were that she was edentulous and had hyperextension of the fingers.

The blood cell count was normal. The blood sugar was 69 mg.; blood chloride, 567 mg.; blood calcium, 8.13 mg., and blood uric acid, 2.36 mg. The total serum proteins were 5.12 gm.; albumin, 3.6 gm., and globulin, 1.51 gm.; A/G ratio was 2.1. The serological test for syphilis was negative.

Urinalysis on admission showed a specific gravity of 1.000 and was negative for albumin and sugar. The average 24-hour output was 5136 cc. After a concentration test of four hours the output diminished, with a specific gravity of 1.006.

An intravenous pyelogram was made before treatment, which demonstrated a rapid elimination of the dye to form a slightly enlarged cystogram. The dye did not have sufficient concentration to outline the kidneys or the ureters.

The skull film was normal.

The treatment is summarized below:

Treatment Type	Symptoms	Sp. Gr.	Albumin	Sugar
1 cc. vasopressin tannate in oil; 5 pressor units intramuscularly	Relief of symptoms ½ hr. after injection; patient noted throbbing sensation in left temporal area for 6 hr.; thirst first appeared after 72 hr.	1.015	Neg.	Neg.
1 cc. vasopressin tannate in oil; 5 pressor units intramuscularly	Symptoms relieved ½ hr. after injection; noted throbbing sensation in left temporal area lasting 8 hr.; could not concentrate; sense of pressure in head; thirst first appeared after 64 hr.	1.021	Neg.	Neg.
Posterior pituitary powder, U. S. P., 40 mg. q. i. d. for 7 days	Symptoms relieved a few minutes after nasal insufflation; severe cough started after 2 days; burning sensation in the chest; temp. to 102 F; powder aggravated the symptoms; cough became almost constant; medication became ineffectual and was discontinued	1.019	Neg.	Neg.
1 cc. vasopressin tannate in oil; 5 pressor units intramuscularly	After untoward symptoms disappeared medication caused severe pruritus; large indurated areas 5 cm. in diameter; cough returned; burning sensation in chest; fell once; symptoms persisted for 3 days; thirst disappeared for 40 hr.	1.017	Neg.	Neg.
0.5 cc. vasopressin tannate in oil intramuscularly	Medication given after symptoms subsided; after medication symptoms increased, with severe pruritus; relieved of thirst for 20 hr.	1.009	Neg.	Neg.
5 units posterior pituitary, U. S. P.	Medication given after symptoms subsided; relief of thirst lasted 4 hr.; marked induration at site of injection; marked pruritus, cough, burning in chest	1.009	Neg.	Neg.
0.01 units of posterior pituitary, U. S. P. increased gradually over 2 wk. to 5 units	Medication given after symptoms subsided; no relief of thirst from first injection; dosage increased each day to cause a small area of induration at site of injection with some pruritus; after 2 wk. 0.1 cc. of obstetrical pituitrin was given without untoward symptoms; thirst slightly decreased with largest dose	1.000	Neg.	Neg.
0.1 cc. pitressin tannate in oil intramuscularly	Relief of thirst for 54 hr. and relief of dryness of the mouth for 30 hr.; throbbing in left temporal area	1.015	Neg.	Neg.
0.25 cc. vasopressin tannate in oil intramuscularly	Relief of thirst for 26 hr.; no untoward symptoms, perspired some	1.012	Neg.	Neg.
0.25 cc. vasopressin tannate in oil intramuscularly	Relief of thirst for 36 hr.; no untoward symptoms	1.016	Neg.	Neg.

This case demonstrates an allergy produced during the course of treatment. The patient showed an allergy to plain posterior pituitary and to vasopressin tannate in oil. Desensitization was carried out with posterior pituitary, U. S. P., diluted with distilled water. It was later possible to give injections of vasopressin tannate in oil. A remarkably small dose, of 0.1 cc., relieved the dryness of the mouth for 30 hours, and real thirst did not return for 54 hours.

The duration of the therapeutic action of vasopressin tannate in oil is related to the thoroughness of mixing before injection.

Case 45.—A 40-year-old white woman was born in Nebraska and lived there until she was 18 years of age. She did not note any excessive thirst until she was in the hospital with her first child. She had lived in the Rocky Mountains for 10 years at this time. She was 28 years of age, and a few days after her first delivery she first noted excessive thirst. She "drank pitchers at a time." A short time after the onset of the symptoms she measured her daily intake to be 20 pt. While in the hospital with subsequent babies she "drank the water off her roses." She stated that after an appendectomy she was "good to everyone just so they would bring water." At present she drinks about two large glasses every

two hours, and at night, only one glass every two hours.

The family history was noncontributory, and no known cases of diabetes insipidus were recognized in the family.

The patient had the usual childhood diseases, and at 16 years of age she had a tonsillectomy. An appendectomy was done at 35 years of age. Her only other significant illness was a sinusitis.

The patient was 60 in. in height and weighed 163½ lb. The temperature was 97 F; pulse rate, 88; systolic blood pressure, 124; diastolic, 80. Results of the physical examination were otherwise normal.

The hemoglobin was 94%, and the white cell count was 12,500.

The urine was water-clear and had a specific gravity of 1.000. It was negative for albumin and sugar.

Treatment was previously carried out by injections of posterior pituitary. The patient was given 1 cc. of vasopressin tannate in oil and had an unusual reaction. The thirst immediately subsided. She developed epistaxis and pitting edema of the legs. She gained 5 lb. in the one day. On the third day she lost the edema and the weight in just a few hours. The patient was then tried on pituitary powder but this was not as effective, and the patient then took ½ ampule of the vasopressin tannate in oil without any untoward symptoms. The urine specific gravity increased to 1.020 on treatment.

CASE 48.—A 19-year-old white female university student had no family history of diabetes insipidus. Her grandfather had diabetes mellitus. The patient had had no unusual childhood diseases and had had a tonsillectomy at 5 years of age. She had never been married.

Her menses started at 13 years of age and are regular. She has a 24-day interval, with a duration of four days. There has been no change in the cycle since the onset of the illness. She did not use tea, coffee, alcohol, or tobacco. At the time of the examination she did not use any medication.

The chief complaint on admission was that of "thirst." The patient stated that she was in an automobile accident on Sept. 25, 1949, at which time she was unconscious from about 6:30 a. m. to 3:30 or 4:30 p. m. She had no headache but did have two "black eyes" and "a bump over the base of the nose." The swelling was more of the right side. She was in the hospital four days and then went back to school. About one and one-half or two weeks following release from the hospital she noted a "sudden onset of thirst." At the time of examination she had to drink water about every two or three hours day and night. She voided about as often as she drank. The weight before the accident was 130 lb., and there had been no change since she came out of the hospital. While in the hospital she vomited considerably.

The physical examination revealed a white woman 66½ in. tall and weighing 125½ lb. The systolic blood pressure was 110; diastolic, 70; pulse rate, 72; temperature, 98.2 F.

Dr. Reed Harrow reported: "The neurological examination on this patient showed a concentric contraction of the visual fields but no bitemporal cutting."

Stereovertical x-ray views to show the base of the skull showed no evidence of fracture or bony abnormality at this time.

The urinalysis showed a specific gravity of 1.004 and was neutral in reaction. It was negative for albumin and sugar. The microscopic examination was negative.

A glucose-tolerance test showed the following results.

Time	Blood Sugar, Mg./100 Cc.	Urine Sugar
Fasting	86	Negative
97 gm. anhydrous dextrose given for 121 lb.		
30 min.	195	Negative
60 min.	235	3+
120 min.	150	Trace
180 min.	52	Negative
240 min.	61	Negative

A B. M. R. at the time Dr. Harrow saw the patient was 0. At examination at the clinic the B. M. R. was—12%.

A glucose-tolerance test done at the Clinic on Jan. 14, 1950, gave results as follows:

Time	Blood Sugar, Mg./100 Cc.	Urine Sugar
Fasting	67.5	Negative
½ hr.	127.5	Negative
1 hr.	145.0	Negative
2 hr.	55.0	Negative
3 hr.	50.0	Negative

A diagnosis of diabetes insipidus was made, and treatment was instituted.

A record of the urine output before treatment is as follows:

	Urine, Cc.		Urine, Cc.
12:45	430	4:15	490
1:30	140	6:55	580
1:35	30	7:10	550
5:30	890	9:30	730
7:45	570	10:25	370
9:45	500	11:30	330
10:50	300	12:40	500
1:25	720		
		Total	6700 cc. in 24 hr.

After 1 cc. vasopressin tannate in oil was given at 11:15 a. m. on Jan. 7, 1950, the thirst left at 11:45 a. m. and did not return until Jan. 9, 1950,

at 6:00 a. m. The output of urine for this time under treatment was as follows:

	Urine, Cc.		Urine, Cc.
4:00 p. m.	240	7:30	230
12:25	370	2:00	250
9:30	290	12:15	300
6:45	460	8:05	290
12:15	290	1:00	520
		5:00	610
	1650	Total	2200 cc.

Posterior pituitary powder, U. S. P., was used and caused sneezing, coughing, and stinging. It was necessary for the patient to take it at the following times to prevent thirst: 11:00, 9:30, 2:00, 8:00, 9:30.

A trial of sublingual Linguets was made. Each tablet contained 30 mg., and the following results on urinary output were found:

	Urine, Cc.	
8:15	550	
10:45	690	
12:30	350	
7:30 a. m.	450	(1 tablet)
8:30	320	
11:00	410	
2:20	770	(1 tablet)
3:00	150	
5:30	820	

The patient used the pills at bedtime and did not get up during the night. She stayed thirsty but could refrain from drinking.

Summary: A diagnosis of post-traumatic diabetes insipidus is made. It is a lifelong disease; no recovery can or should be anticipated. The only satisfactory treatment found for this patient is that of vasopressin tannate in oil, which will have to be given about every 36 hours for the rest of her life.

Case 49.—A 30-year-old white male farmer had no family history of diabetes insipidus. The family history was negative for cancer, tuberculosis, diabetes, epilepsy, hypertension, and migraine.

The patient married at 20 years of age. He had had 4 children, the oldest a boy 9 years of age, the second a boy 8 years of age, the last two, twins, 4 years of age, a boy and a girl.

The patient drank 4 cups of coffee daily and beer only occasionally. He had the usual childhood diseases, with no serious complications. He had tonsillectomy at 8 years. At the age of 26 he was in a car accident. He sustained momentary unconsciousness and an injury to the left side of the head.

The chief complaint on admission was "always dry and can't drink enough water." The onset of the symptoms had been quite sudden and had appeared four months before admission. He had sustained no injury immediately preceding it. He had had no recent cold or elevated temperature. He had noted some "twitching of the muscles and dizzy spells at times." He had lost 10 lb. since the onset of the illness.

The physical examination revealed a white man 69 in. tall and weighing 150 lb. The systolic blood pressure was 140; diastolic, 80; pulse rate, 92; temperature, 99.2 F. The visual fields were grossly normal, and results of the rest of the examination were normal.

The urinalysis showed a 24-hour output of 9600 cc.; specific gravity, 1.002; neutral reaction, and no albumin or sugar. The microscopic examination was negative.

The blood examination revealed hemoglobin, 12.10 gm.; RBC, 5,210,000, and WBC, 11,350. The differential white cell count showed 71% neutrophiles, 1% eosinophiles, and 28% lymphocytes. The total protein was 7.04 gm. per 100 cc. The A/G ratio was 4.29:2.75. The serum cholesterol was 149 mg. per 100 cc.

After treatment of 1 cc. of vasopressin tannate in oil the 24-hour urine output was 1210 cc. The color was dark yellow; the specific gravity, 1.013, and it was neutral in reaction. It was negative for albumin and sugar.

Stereoscopic left lateral views of the skull with a posteroanterior and a Towne view showed the sella to be razor-sharp in outline, without decalcification (Figs. 43 and 44). This finding suggested early erosion changes secondary to increased intracranial pressure. At the junction of the coronal and saggital sutures was a large ragged erosion, largely in the inner table and also extending into the outer table, measuring about 5×6 cm. The erosion was slightly to the left of the midline in its

Figure 43 (Case 49).

major portions. At the inferior portion of each parietal bone was an area of radiolucency roughly 2 cm. in diameter. Two smaller areas of radiolucency were present in the left frontal bone, each measuring 1 cm. across. These latter areas gave the definite impression of having been either trephine holes or areas of erosion followed by recalcification of the skull in those areas. No abnormal intracranial calcification could be seen.

Opinion: The areas of radiolucency in the parietal bones and left frontal bones could well be on the basis of either ancient trephine holes or a process such as xanthomatosis with subsequent incomplete healing.

Stereoscopic posteroanterior views of the chest showed the parenchyma of each lung to be normal. The heart and thoracic skeleton were normal.

A fluoroscopic survey of the skeleton, while admittedly inadequate, showed no gross lesions in the

Figure 44 (Case 49).

skeletal system other than the ones described in the calvarium.

An encephalogram showed subarachnoid pathways to have filled and to appear normal. The ventricular system was not, however, filled. Air along the falx indicated that it was not displaced.

Spinal fluid examination revealed a white cell count of six per cubic millimeter, with a differential count of one polymorphonuclear cell and five lymphocytes. The gold curve was normal. The total protein was 15 mg. per 100 cc. The serological test for syphilis was negative.

A biopsy of the skull was reported as follows: "The specimen consists of two pieces of tissue measuring together $1\times0.5\times0.5$ cm. The tissue is moderately firm and fibrocellular in consistency and red to yellow-gray in color.

"Section shows areas of fibrous tissue infiltrated with lymphocytes, monocytes, and large lipoid cells

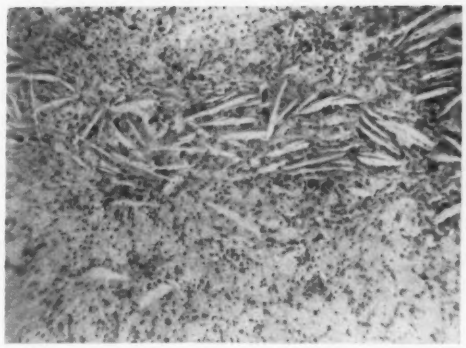


Figure 45 (Case 49).

with pale, slightly granular cytoplasm and small dark eccentric nuclei. Some areas consist almost entirely of these large phagocytes. In one section are sharply defined linear spaces (the so-called cholesterol clefts [Figs. 45 and 46]).

"Some fragments consist of eosinophilic fibrous tissue but there is nothing identifiable as bone."

Pathological diagnosis: Xanthoma of the skull consistent with Hand-Schüller-Christian disease.

Case 52.—A 13-year-old white male student was born of a normal delivery. His mother, her mother, and her father had no knowledge of the disease being present in the family.

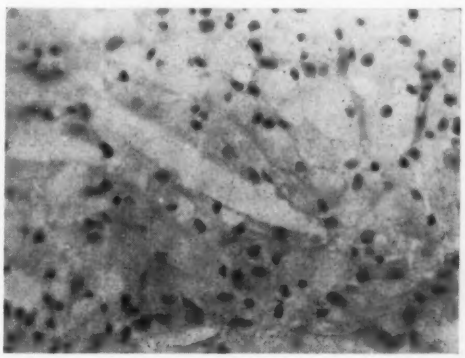
The patient had measles at 3 years of age and at 6 years of age was struck on the head by a pole that caused a laceration over the left perietal area.

The patient was considered normal until about 7 years of age, at which time he passed a 12 in. round worm. He was given medication for the worms and shortly thereafter started "craving water." At this time he also noted enuresis. Since the onset he has had to drink water every two hours day and night. He drinks two glasses at a time.

The physical examination was normal.

He responded well to antidiuretics.

Figure 46 (Case 49).



CASE 55.—A 19-year-old white male student had not previously heard of the disease, and no member of his family had the disease.

The family history was negative. His habits were moderate. As a child he had had uncomplicated chicken-pox, mumps, and measles.

The chief complaint was excessive thirst and urination.

The history that may be related to the illness dates back to when the patient was 15 years of age, when he was struck in the right parietal region with a baseball bat. This injury required five sutures. There was no loss of consciousness. At the age of 17 years a saddlehorse fell on him and fractured his leg. At 7 years of age he had his nose broken. He had a tonsillectomy and adenoidectomy at 3 years of age.

About two to three weeks after the fracture of his left leg, and after he had been on crutches for one week, he noted a sudden onset of excessive thirst and urination. His average intake since the onset had been three to four large glasses of water every two hours.

The patient was a well developed youth 67½ in. tall and weighing 140 lb. The systolic blood pressure was 120; diastolic, 70; pulse rate, 70; temperature, 98.2 F.

The Kahn test was negative, and the blood group, A, Rh-negative.

The sella turcica was found to be normal on x-ray examination.

The urine had a specific gravity of 1.004 and was neutral in reaction. It was negative for albumin and sugar. The hemoglobin was 11.7 gm. and was 75%; RBC, 4,240,000; WBC, 8400.

The serum protein was 5.9 gm.; the albumin, 3.6 gm., and the globulin, 2.3 gm.; A/G ratio, 1.56.

CASE 56.—A 24-year-old white woman had no family history of diabetes insipidus. The patient had never married, and her menstrual history was normal. Her habits were normal, and she had had no operations.

Her chief complaint was excessive thirst whose onset was eight months previous to the examination. The onset was gradual and was not preceded by any known infection or injury. The patient had noted some headaches recently. Her 24-hour output of urine was 13½ quarts.

Physical examination revealed a height of 63 in. and a weight of 110½ lb. The systolic blood pressure was 110; diastolic, 70; pulse rate, 68; temperature, 98.2 F.

The sella turcica was normal to x-ray examination. The Kahn test was negative. The blood type was A, and the Rh factor was positive.

CASE 58.—A 33-year-old white housewife first noted excessive thirst at the age of 23 years. The symptoms came on "over night." When she first started treatment she noted severe headaches.

The patient married at 27 years and has had three children and five miscarriages. Her menstrual history has been normal. Her habits are moderate, but she does use alcohol, which is unusual in diabetes insipidus.

She had the usual childhood diseases without complications.

Physical examination revealed a well-developed white woman 66 in. tall and weighing 173 lb. The systolic blood pressure was 120; diastolic, 70; pulse rate, 68; temperature, 98.4 F. Otherwise the examination was completely normal.

The blood examination and the urinalysis were both normal. The serological test for syphilis was negative. The blood was Type A and was Rh-positive.

The skull was found to be normal on x-ray examination. The sella turcica was normal in size and shape.

The patient responded well to vasopressin tannate in oil.

CASE 59.—During the six months preceding the examination the patient had noted a gradual onset of increasing nervousness and excessive thirst and urination.

The past history was negative except that he had lived in France for two years. He had an appendectomy; otherwise the medical history was negative.

The patient was of normal build and weighed 152 lb. The systolic blood pressure was 100; diastolic, 50; pulse rate, 60; temperature, 98 F.

The blood cell count and urinalysis were both normal. The serological test for syphilis was negative. The blood phosphorus was 3.45 mg. per 100 cc., and the calcium was 12.8 mg. per 100 cc. of blood.

The skull x-ray was normal.

The symptoms were immediately relieved by the administration of vasopressin tannate in oil.

CASE 60.—The patient was a 30-year-old white housewife. There was no family history of diabetes insipidus. Symptoms of excessive thirst and urination were sudden in onset. No known infection had preceded this except for a severe headache.

The patient married at 18 years and she has had two children and one miscarriage. Her menstrual history has been normal.

Her habits have been moderate and the only medication she had taken previous to the onset was vitamin B_{12}. She had had no operations.

The physical examination was normal. The patient was 65¾ in. tall and weighed 136 lb. The systolic blood pressure was 120; diastolic, 70; pulse rate, 82; temperature, 97.6 F.

The blood cell count and urinalysis were normal. The serological test for syphilis was negative. The x-ray of the skull was normal.

REFERENCES

Owing to inaccessibility of some references and original articles, the entire bibliography of the article by Bullock is given because of the completeness of his study concerning the hereditary type of diabetes insipidus.

1. de Lange, C.: Über erblichen Diabetes insipidus, Jahrb. Kinderh. **95**:1-14, 1935.

2. Janzen, E., and Broekman, J.: Hereditary Diabetes Insipidus, Nederl. tijdschr. geneesk. **1**: 2519, 1921; abstracted, J. A. M. A. **77**:330 (July 23) 1921.

3. Bullock, W.: Diabetes Insipidus, in The Treasury of Human Inheritance, London, Dulau & Co., 1909, Vol. 1, Sect, 1-A, p. 575. This article gave the family trees and summarized the following original articles:

(*a*) Weil, A.: Über die hereditäre Form des Diabetes insipidus, Arch. path. Anat. **95**:70, 1844.

(*b*) Weil, A.: Über die hereditäre Form des Diabetes insipidus, Deutsch. Arch. klin. Med. **93**: 180, 1908.

(*c*) Lauritzen, M.: Om hereditaer Diabetes insipidus, Hosp.-Tid. **1**:353; 392; 423; 451, 1893.

(*d*) Pain, G.: Notes à propos de quelques observations de polyurie chronique, Thesis, Paris, 1879, p. 19.

(*e*) Orsi, F.: Sei individui d'una stessa famiglia colpiti da idruria, Gazz. med. ital. lomb. **3**:352, 1881.

(*f*) Lacomb, L. V.: De la Polydipsie, Paris, 1841; abstracted, Expérience **7**:305; 323; 339; 353; 385, 1841.

(*g*) Clay, R. H.: Three Cases of Diabetes Insipidus in One Family, Lancet **1**:1188, 1889.

(*h*) Deebrey: Observation de polyurie, Gaz. hôp. Paris, p. 546, 1895.

(*i*) McIlraith, C. H.: Notes on Some Cases of Diabetes Insipidus with Marked Family and Hereditary Tendencies, Lancet **2**:767, 1892.

(j) Reith, A.: Polydipsia: Treatment by Large Doses of Valerian; Improvement; Clinical Remarks, M. Times & Gaz. **1**:309, 1866.

(*k*) Wachsmuth, H.: Ein Fall von Diabetes insipidus, Arch. path. Anat. **26**:318, 1863.

(*l*) Knopfelmacher: Diabetes insipidus der Kindern, Munch. med. Wchnschr. No. 13, p. 629, 1905.

(*m*) Sasse, C.: Ein neuer Fall von hereditärem Diabetes insipidus, Inaugural Dissertation, Bonn, J. Bach Wwe., 1893.

(*n*) Gee, S.: A Contribution to the History of Polydipsia, St. Bartholomew's Hosp. Rep. **13**:79, 1877.

(*o*) Lanceraux, E.: De la Polyurie (diabète insipide), Thesis, Paris, 1869.

(*p*) Meyer, E.: Über Diabetes insipidus und andere Polyurien, Deutsch. Arch. klin. Med. **83**:1, 1905.

(*q*) Seiler, R.: Über das Wesen des Diabetes insipidus, Ztschr. klin. Med. **61**:1, 1907.

(*r*) Nothnagel, C. W. H.: Specielle Pathologie und Therapie, Vol. 7, Part 7, Wein, 1899.

(*s*) A System of Medicine, edited by T. C. Allbutt and H. D. Rolleston, London, Macmillan & Co., Vol. 3, 1907, p. 167.

(*t*) Roberts, W.: A Practical Treatise on Urinary and Renal Diseases, Including Urinary Deposits, Ed. 4, London, Smith, Elder & Co., 1885.

4. Chase, L. A.: Hereditary Diabetes Insipidus, Canad. M. A. J. **17**:212-214 (Jan.) 1927.

5. Chester, W., and Spiegel, L.: Hereditary Diabetes Insipidus, J. A. M. A. **100**:806-809 (March 18) 1933.

6. Lhermitte, J.: La polyurie infundibulaire: Le Diabète insipide syphilitique, Ann. méd. **11**:89, 1922; abstracted, J. A. M. A. **78**:1576 (May 20) 1922.

7. Marañón, G., and Bonilla, E.: A Case of Precocious and Hereditary Diabetes Insipidus, Endocrinology **9**:467, 1925.

8. Levit, S. G., and Pessikova, L. N.: Diabetes Insipidus: Heredity, Genetics and Its bearing on the Problem of Dominance in Man, J. Hered. **27**: 445-448, 1936.

9. Barach, J. H.: Diabetes Insipidus, Am. J. M. Sc. **154**:220 (Aug.) 1917.

10. Graham, E. A.: Spinal Puncture in Diabetes Insipidus, J. A. M. A. **69**:498 (Nov. 3) 1917.

11. Hall, G. W.: Diabetes Insipidus: A Case Report Following Epidemic Encephalitis with Enormous Polyuria, Am. J. M. Sc. **165**:551-562 (April) 1923.

12. Gänsslen and Fritz: Über Diabetes insipidus, Klin. Wchnschr. **3**:22-23 (Jan. 1) 1924; abstracted, J. A. M. A. **82**:588 (Feb. 16) 1924.

13. Blotner, H.: The Inheritance of Diabetes Insipidus, Am. J. M. Sc. **204**:261-265 (Aug.) 1942.

14. Canelo, C. K., and Lisser, H.: A Case of Diabetes Insipidus Controlled with Powdered Pituitary Posterior Lobe Extract Applied Intranasally, as Snuff, California & West. Med. **42**: 178-180 (March) 1935.

15. Brown, W. E., Jr., and Rynearson, E. H.: A Procedure for the Diagnosis of Diabetes Insipidus, Proc. Staff Meet., Mayo Clin. **19**:67-68 (Feb. 9) 1944.

16. MacCallum, W. G.: A Textbook of Pathology, Ed. 6, Philadelphia, W. B. Saunders Company, 1937.

17. McGavick, T. H.; Boyd, L. J., and Gilvin, P: Experimental Modification of Water and Salt Output in Patients with Diabetes Insipidus, J. Clin. Endocrinol. **2**:551-559 (Sept.) 1942.

18. Sprunt, T. P.: Diabetes Insipidus, in Cecil, R. L.: Textbook of Medicine, Ed. 4, Philadelphia, W. B. Saunders Company, 1938.

19. Best, C. H., and Taylor, N. B.: Diabetes Insipidus, in The Physiological Basis of Medical Practice: A University of Toronto Text in Applied Physiology, Baltimore, William Wood & Company (Division of Williams & Wilkins Company), 1937.

20. Richter, C. P.: Experimental Diabetes Insipidus, Brain **53**:76, 1930.

21. Just, G.: Ein Wort zu Weils Diabetes insipidus-Stammbaum, Arch. Rassenb. **16**:312, 1924-1925.

22. Blumgart, H. L.: The Antidiuretic Effect of Pituitary Extract Applied Intranasally in a Case of Diabetes Insipidus, Arch. Int. Med. **29**: 508 (April) 1922.

23. Flint, A.: Diabetes Insipidus, in A Treatise on the Principles and Practice of Medicine, Ed. 4, Philadelphia, H. C. Lea, 1873.

24. Green, J. A., and January, L. E.: Diabetes Insipidus: Treated by the Subcutaneous Administration of a Suspension of Pitressin Tannate in Oil, J. A. M. A. **115**:1183-1185 (Oct. 5) 1940.

25. Jones, G. M.: Diabetes Insipidus: Clinical Observations in 42 Cases, Arch. Int. Med. **74**: 81-93 (Aug.) 1944.

26. Wohl, M. G., and Larson, E.: Diagnosis and Treatment of Pituitary Gland Disorders, M. Clin. North America **26**:1657-1678 (Nov.) 1942.

27. Alpers, B. J.: Diagnosis and Treatment of Pituitary Tumors, M. Clin. North America **26**: 1679-1696 (Nov.) 1942.

28. Williams, R. H., and Henry, C.: Nephrogenic Diabetes Insipidus: Transmitted by Females and Appearing During Infancy in Males, Ann. Int. Med. **27**:84-95 (July) 1947.

29. MacBryde, C. M.: Signs and Symptoms, Ed. 2, Philadelphia, J. B. Lippincott Company, 1952.

30. Smith, H. W.: The Kidney, New York, Oxford University Press, 1951.

Case Reports

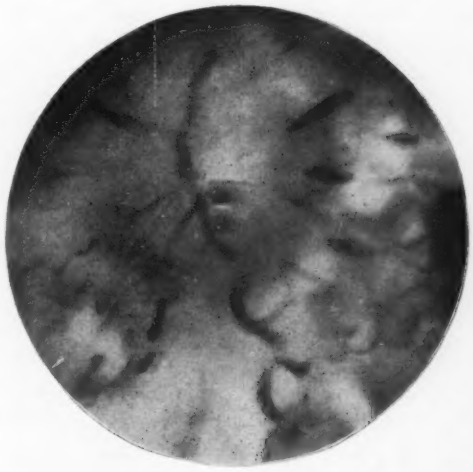
REFRACTORY HYPOTENSION FOLLOWING REMOVAL OF PHEOCHROMOCYTOMA

EARL F. BEARD, M.D.
DONALD B. BUTLER, M.D.
and
HARVEY S. ROSENBERG, M.D., Houston, Texas

SINCE pheochromocytoma has been widely recognized clinically as a cause of hypertension, many unusual aspects of this tumor and the clinical syndrome it produces have been reported. These have included errors in diagnosis, false negative and false positive pharmacologic tests, and extra-adrenal location of the tumor.* The case to follow illustrates another unusual aspect of the clinical syndrome, the requirement of massive doses of arterenol (Nor-epinephrine) following surgical removal of pheochromocytoma. The management of patients with pheochromocytoma before, during, and after surgery has recently been reviewed by Sprague and others,[4] and the usual methods of vasopressor maintenance will not be reviewed here. The following case illustrates the failure to maintain a normal postoperative blood pressure until massive doses of arterenol were used.

The patient was an 11-year-old white boy first seen in September, 1954, because of weight loss, easy fatigability, lassitude, and night sweats of approximately three months' duration. His past history was not remarkable. He had always been somewhat irritable, but he was more so during the preceding three months. In June, 1954, the patient had weighed 78 lb., but there had been a weight loss of 8 lb. during the summer. No history of paroxysmal headache or palpitation could be obtained, but at times he would awaken during the night with dyspnea, anxiety, and profuse sweating. The patient had progressively failing vision for two months. On examination the blood pressure was 170 mm. Hg systolic and 140 diastolic, with a pulse rate of 140. The oral temperature varied between 98.0 and 99.0 F. The patient appeared emaciated and chronically ill. There was a fine miliary rash over the body. The heart was enlarged to the midaxillary line, and there was a gallop rhythm at the apex. The optic fundi showed diffuse and focal arteriolar constrictions, numerous exudates, and bilateral papilledema. Figure 1 shows a portion of the right optic fundus. Urinalysis was normal; Kline test was negative, and the sedimentation rate was 20 mm. in an hour. The erythrocyte count was 4,720,000; the hemoglobin, 13.2 gm., and the leucocyte count was 10,400, with 57% segmented neutrophiles, 32% lymphocytes, and 1% monocytes. The blood urea nitrogen was 15 mg. per 100 cc., and sulfobromophthalein (Bromsulfalein) and phenolsulfonphthalein tests were within normal limits. Roentgen examination of the chest revealed cardiac enlargement, and an electrocardio-

Fig. 1.—Photograph of a portion of the right optic fundus, illustrating papilledema and numerous exudates in the immediate vicinity of the optic disk.



Submitted for publication May 5, 1955.

From the Medical, Surgical, and Laboratory Departments of Texas Childrens Hospital.

* References 1-3.

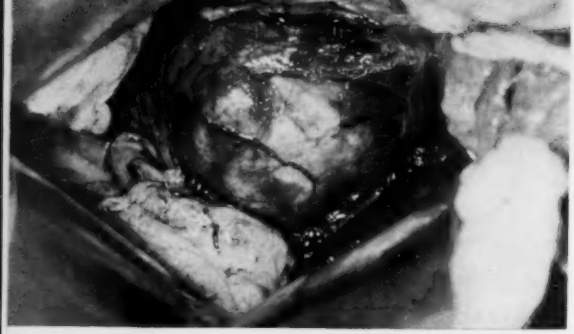


Fig. 2.—Tumor of left adrenal gland as exposed at surgery.

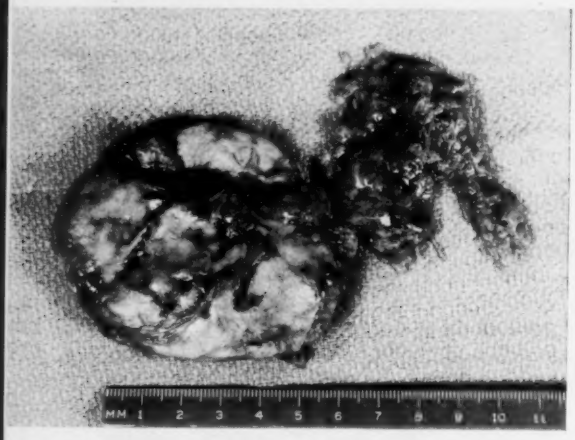
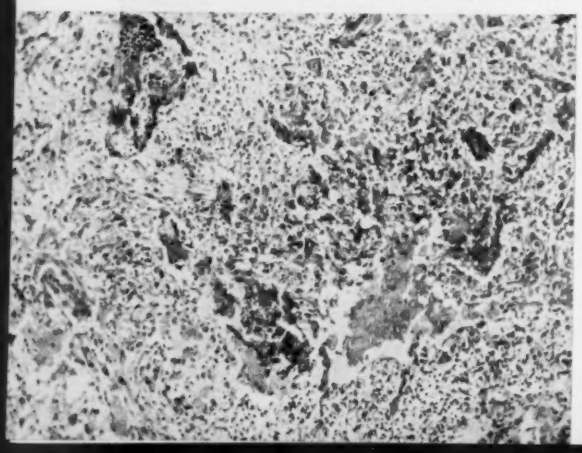


Fig. 3.—The surgical specimen, showing its cystic nature and thin wall. The contents, shown extruded above, were red-gray, soft, necrotic, and friable.

gram showed typical changes of left ventricular hypertrophy. An intravenous pyelogram was essentially within normal limits, but the left kidney was depressed and slightly rotated.

An intravenous phentolamine (Regitine) test done with 2.5 mg. of phentolamine methanesulfonate showed a drop in blood pressure from control levels of 170 mm. Hg systolic and 130 diastolic to 124 mm. Hg systolic and 84 diastolic in one and one-half minutes. This test was repeated on another occasion, and at this time 1 mg. of phentolamine methanesulfonate intravenously produced a fall in blood pressure from control levels of 200 mm. Hg systolic and 160 diastolic to 140 mm. Hg systolic and 112 diastolic in two minutes. A repeat injection of 2.5 mg. of phentolamine methanesulfonate after the pressure had returned to 175 mm. Hg systolic and 145 diastolic caused a second drop to 122 mm. Hg systolic and 80 diastolic within two minutes. After the pressure had again returned to 160 mm. Hg systolic and 130 diastolic, 10 mg. of piperoxan hydrochloride was given intravenously, and the blood pressure dropped to 110 mm. Hg systolic and 85 diastolic. These responses were considered to represent positive pharmacologic tests for pheochromocytoma. Because of the apparent congestive heart failure and episodes of pulmonary edema, the patient was digitalized, and, in preparation for surgery, 100 mg. of cortisone acetate was given intramuscularly each day for three days preoperatively.

Fig. 4.—Microscopic section of the tumor stained with hematoxylin and eosin. The cellular pattern and marked vascularity are apparent. A "lake" of chromaffin material is present. The dark-staining cells are filled with chromaffin granules.



On Oct. 14, 1954, operation was performed by the transabdominal route to explore the adrenal areas. During the induction of anesthesia, acute pulmonary edema occurred and was controlled by intravenous lanatoside C and the blood pressure rose markedly but was easily controlled with phentolamine methanesulfonate by continuous intravenous drip. A tumor, approximately 7.5 mm. in diameter, was found involving the left adrenal gland (Fig. 2). As soon as the tumor had been isolated from its blood supply, the blood pressure fell precipitously, and arterenol in a concentration of 8 mg. per liter of solution was started at an infusion rate of 40 to 60 drops (0.25 to 0.37 ml.) per minute. However, the blood pressure remained unobtainable for approximately two minutes, and it was only after 6 mg. of arterenol had been given intravenously without dilution that the pressure rose. The concentration in the infusion was increased to 40 mg. per liter of solution at infusion rates of 40 to 60 drops per minute, and the arterial blood pressure could then be maintained at levels of approximately 100 mm. Hg systolic and 60 diastolic.

The surgical specimen (Fig. 3) weighed 90.0 gm. and measured 7.5 by 5.7 by 1.5 cm. The structure was cystic in nature and had been artefactually ruptured, revealing the contents of the cyst to be soft, red-gray, and friable.

Microscopic preparations were made from tissue that had been fixed in Helly's fixative, Orth's fixative, 10% neutral formalin, and fresh frozen material. Stains included hematoxylin and eosin, periodic acid-Schiff, and Gomori's Giemsa. Arch-

itecturally, the tissue consisted of denisely cellular sheets that were incompletely divided by thin vascular trabeculae (Fig. 4). Necrosis and hemorrhage were prominent. The neoplastic elements were identified intravascularly as well as within the capsule.

Cystologically, there was considerable variation in structure, with individual cells ranging from elongated units with streamers of cytoplasm to those which were round and symmetrical with an almost pavement-like regularity. Granules were identified irregularly within the cytoplasm, particularly in the Orth-fixed material. These granules were readily stained by Gomori's Giemsa method. A small number of the granules were periodic acid-Schiff-positive (Fig. 5).

It is probably not possible to distinguish between benign and malignant varieties of this tumor on histologic grounds alone. As pointed out by Stout,[5] most of these tumors are benign and rarely metastasize despite the presence of intravascular invasion.

Following surgery, it was necessary to continue intravenous arterenol in the same concentration (40 mg. per liter) in order to maintain the blood pressure at levels of approximately 100 mm. Hg systolic and 80 diastolic. Because it was felt that acute adrenal cortex insufficiency might be present in spite of preoperative cortisone preparation, 100 mg. of hydrocortisone was given intravenously approximately eight hours after operation, but this made no appreciable difference in the requirements for arterenol. Electrocardiogram at this time revealed normal rhythm with left ventricular strain. Approximately 12 hours postoperatively, however, the blood pressure began to respond more readily to the arterenol solution and it was possible to reduce the concentration to 32 mg. per liter of solution given at an infusion rate of 30 to 40 drops (0.09 to 0.25 ml.) per minute. Approximately 15 hours postoperatively, when his condition seemed more favorable than at any time since surgery (as judged by a better blood pressure response, absence of signs of congestive heart failure or shock, and his conscious recognition of relatives), the patient suddenly gasped, became apneac and cyanotic, and died. In all, he had received a total of 128 mg. of arterenol during and after the operative procedure.

Postmortem examination revealed slight bilateral pulmonary edema, marked left ventricular hypertrophy of the heart (the left ventricle measuring 12 mm. in thickness), early atherosclerosis of the abdominal aorta, and some atherosclerosis about the coronary ostia. There was no evidence of myocardial infarction. The operative site of the left adrenalectomy appeared satisfactory, and there was no evidence of hemorrhage in the abdominal cavity or elsewhere. The right adrenal gland was intact, and though somewhat small (5 gm.) it did not appear atrophic.

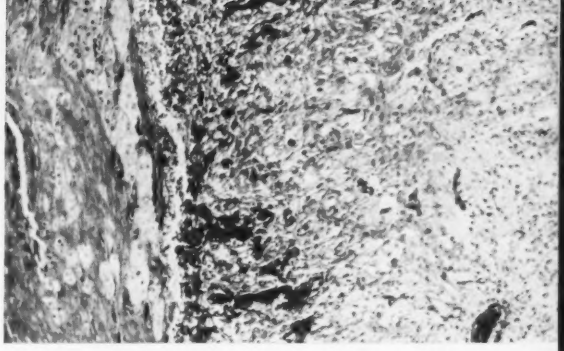


Fig. 5.—Microscopic section of the surgical specimen stained with periodic acid-Schiff stain. The fibrous capsule is shown with the few large clear cells interpreted as the remnants of the adrenal cortex. The dark-staining material is made up of periodic acid-Schiff-positive granules.

COMMENT

The preceding case of pheochromocytoma appears unusual in the massive requirements of the patient for arterenol following removal of the tumor. This occurred in spite of the absence of hemorrhage and in spite of preoperative preparation which should have been more than adequate to prevent adrenal cortex insufficiency. The mechanism of death is unexplained in this case, but, in the absence of significant postmortem findings, it is suspected that death was due to a sudden cardiac arrhythmia, most likely ventricular fibrillation. Although it is generally recognized that arterenol in the usual dosage range does not cause increased myocardial irritability,[6] one might wonder if this is also true when large doses are required in the patient receiving digitalis and whose myocardium might be subjected to some hypoxia during anesthesia. It is therefore suggested that administration of quinidine or other depressants of myocardial irritability might be considered when large doses of arterenol must be given to such patients.

SUMMARY

An 11-year-old boy with a malignant pheochromocytoma of the left adrenal gland was subjected to adrenal resection. A 90 gm. tumor of the left adrenal was excised, and the

postoperatve course was remarkable in that a total of 128 mg. of arterenol was required during the 12 hours postoperatively, until the patient's sudden death. This represents a dose of 1.8 mg. per pound of body weight to maintain normotensive blood pressure.

REFERENCES

1. Ross, R. D.: False Positive Reaction to the Regitine Test for Pheochromocytoma, Ann. Int. Med. **41**:1061-1066 (Nov.) 1954.

2. Gibbs, D. F., and MacLean, N.: Extraadrenal Pheochromocytoma Exhibiting a False-Negative F 933 Test, Ann. Int. Med. **38**:1069-1080 (May) 1953.

3. Soffer, A.: False Positive Reaction to the Piperoxane Hydrochloride Test for Pheochromocytoma, J. A. M. A. **148**:538-541 (Feb. 16) 1952.

4. Sprague, R. G.; Kvale, W. F., and Priestley, J. T.: Management of Certain Hyperfunctioning Lesions of the Adrenal Cortex and Medulla, J. A. M. A. **151**:629-639 (Feb. 21) 1953.

5. Stout, A. P.: Tumors of the Peripheral Nervous System, in Atlas of Tumor Pathology, Washington, D. C., Armed Forces Institute of Pathology, 1949, Sec. II, Fascicle 6.

6. Miller, A. J.; Shifrin, A.; Kaplan, B. M.; Gold, H.; Billings, A., and Katz, L. N.: Arterenol in Treatment of Shock, J. A. M. A. **152**:1198-1201 (July 25) 1953.

TOXIC NEPHROSIS AND MASSIVE HEPATIC NECROSIS PRODUCED BY URETHAN

JOHN F. FLANAGAN, M.D., Emory University, Ga.

URETHAN since 1946 has been used extensively in the treatment of multiple myeloma with a good palliative response in somewhat more than 50% of the cases. The margin of safety in the use of this chemotherapeutic agent has appeared to be fairly broad. Moderate leucopenia and gastrointestinal symptoms are the most frequent complications. Rare reports have appeared of agranulocytosis and aplastic anemia in patients on urethan, and reversible central nervous system symptoms have been described, with improvement following cessation of therapy.[6] In the past few years convincing evidence has accumulated from both experimental and clinical data indicating that in the dosage range required for effective therapy urethan may occasionally produce massive hepatic necrosis.* Five cases of acute massive centrilobular liver necrosis in patients with multiple myeloma on this treatment have been reported in the last five years.† Findings suggestive of renal damage produced by urethan have been reported in only one previous case.[2] This patient with myeloma had been treated for 17 days at a dosage of 4 gm. daily. He developed hematuria and albuminuria, which cleared following cessation of treatment. No histologic studies of the renal lesion were described.

Submitted for publication May 26, 1955.

From Department of Pathology, Emory University School of Medicine, Emory University.

* References 1-5.

† References 2 and 3-5.

Our patient with proved multiple myeloma was treated with urethan at a dosage of 2 to 4 gm. daily for 10½ months. The patient died in hepatic failure, and at autopsy massive acute centrilobular liver necrosis resembling the findings in previously reported cases of urethan toxicity was found. In addition, marked tubular injury was present, which also appeared to result from the toxic effects of this compound.

REPORT OF A CASE

A 39-year-old white male engineer suffered a fracture of the first lumbar vertebra in August, 1953, while diving into a swimming pool. Early in 1954 he developed an "infected lesion" in the nose and was noted to have a protuberance of the left frontal bone above the supraorbital ridge. Biopsy from the nares and from the frontal bone in March, 1954, showed extensive infiltration by anaplastic plasma cells. A skeletal survey by roentgenogram revealed multiple osteolytic lesions of the skull, humeri, pelvis, and femoral heads. Marrow aspiration from the sternum showed 90% replacement by atypical plasma cells. On March 11, 1954, he was placed on urethan therapy at a dosage of 2 to 4 gm. daily. This medication was maintained, with only a single interruption, until death, 10½ months later.

In addition, he received a short period of triethylene melamine therapy totaling 37.5 mg. by the last of November, 1954. No triethylene melamine was taken in the last two months except for a single 2.5 mg. tablet ingested on the day before death. Local roentgen therapy was given to the skull, nasal septum, and dorsal spine. On this therapeutic regimen he improved considerably, with diminution in back pain and maintenance of a good hemoglobin level to the terminal phase of illness and with a fall in serum globulin from 10.4 gm/100 ml. at the beginning of treatment to 7.5 gm/100 ml. three weeks before death. His course was complicated by the development of pneumococcal meningitis in December, 1954. He was treated successfully

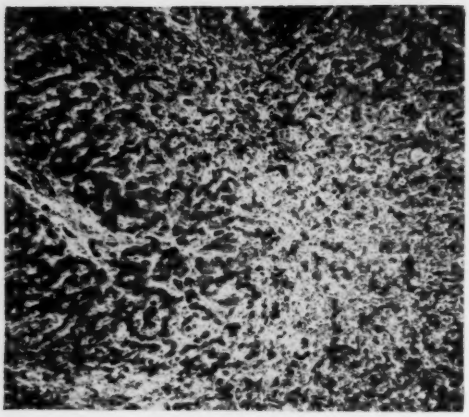


Fig. 1.—Liver with extensive centrilobular and midzonal necrosis. Phloxine and methylene blue; reduced about ¼ from mag. × 90.

with penicillin potassium 16,000,000 units daily for 14 days. Moderate jaundice was noted during this infection, and the total serum bilirubin rose to 5.4 mg/100 ml. on Dec. 13, 1954. Urethan therapy was stopped temporarily during this episode of meningitis and was restarted Dec. 28, 1954, at a dosage of 1 gm. daily. This dosage was later raised to 4 gm. daily. Cortisone was begun at a dosage of 100 mg. daily on Jan. 20, 1955, and apparently a single triethylene melamine tablet was taken on Jan. 21, 1955. He was readmitted in shock on Jan. 22, 1955, with a history of hematemesis of 30 minutes' duration. Laboratory data showed a hemoglobin of 14.0 gm/100 ml. with moderate reduction in platelets. A transfusion of 1000 cc. of whole blood was given, followed by prompt return of the blood pressure to normal. On Jan. 23, 1955, progressive stupor developed. At the same time, jaundice was first noted, which increased rapidly until the patient died, on Jan. 25, 1955. The serum bilirubin six hours before death was 6.6 mg/100 ml., and the NPN determined at the same time was 54 mg/100 ml. No urinalysis was performed.

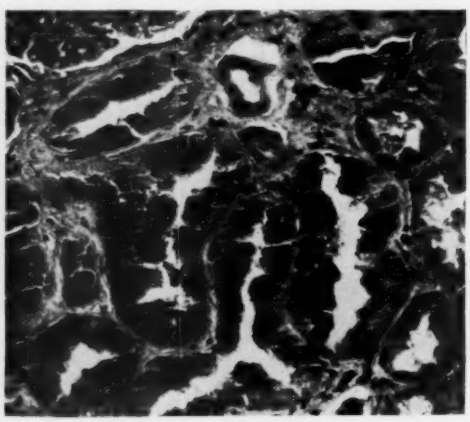
Autopsy.—Gross Findings: The most significant autopsy findings involved the liver and kidneys. The liver weighed 1350 gm. The hepatic parenchyma on cut surface was coarse and reddish to grayish-yellow, with indistinct lobular marking. The consistency was firm. The gall bladder and biliary tract were not remarkable. The left kidney weighed 227 gm., and the right kidney, 226 gm. Both kidneys showed a smooth pale yellowish surface. The consistency was flabby. On cut surface the usual landmarks were indistinct and the parenchyma bulged from beneath the capsule. The renal calyces and pelves were not remarkable.

Additional gross findings included moderate icterus of the sclerae and 3600 cc. of greenish fluid in the peritoneal cavity. The base of the lower lobe of the left lung posteriorly was reddish purple and firm. The mucosa of the stomach showed numerous diffuse petechial hemorrhages, while the jejunum and ileum contained a considerable amount of grayish to black material having the appearance of partially digested blood. Marrow removed from the sterum, rib, and spine was deep purple and was mushy in appearance.

Histologic Findings: The general architecture of the liver was well preserved. The lobules displayed extensive necrosis, beginning in the centrilobular areas and frequently extending to the midzonal or even to peripheral portions (Fig. 1). In the involved areas the liver cells showed changes ranging in appearance from deeply acidophilic hyalin clumps within the cytoplasm to complete necrosis with persistence of the ghost-like outlines of degenerating cells. Bile stasis was present in the canaliculi of the less-involved parenchymal cells. The lesion was attended by little inflammatory cell infiltration, although hemorrhage was frequently present. The sinusoidal endothelium showed no demonstrable injury. The Kupffer cells appeared prominent and often showed phagocytic activity. There was no fatty metamorphosis. The portal spaces appeared unaltered and revealed no infiltration by plasma cells. The blood vessels in all areas were congested. Thrombi were not encountered.

The kidneys revealed diffuse alteration of the tubular epithelium in all nephrons (Fig. 2). Localization of this lesion in the nephron was difficult. The only certain conclusion was that the portions

Fig. 2.—Marked cytoplasmic dispersion of the epithelium in many renal tubules. Only segments of Henle's loop are not involved. Phloxine and methylene blue; reduced about ¼ from mag. × 210.



of the loops of Henle in the medulla and the collecting tubules were not involved. The tubular epithelial cells were large and displayed a uniformly acidophilic and finely granular dispersion of the cytoplasm. The granular material did not react with either the periodic acid-Schiff or fat stain. The nuclei of these cells appeared normal. Occasional tubules contained dense acidophilic casts without attending cellular reaction or giant-cell formation. The glomeruli and other blood vessels were not altered except for the presence of granular acidophilic clumps of protein material in many of the capillaries and veins. The tubular basement membranes, the interstitial connective tissue, and the structures of the pelvis were not remarkable.

Additional histologic findings included aspiration of gastrointestinal contents and bronchopneumonia of the lower lobe of the left lung. Marrow from the ileum, rib, and thoracic vertebra showed almost total replacement by anaplastic plasma cells, and a few scattered atypical plasma cells were present in the spleen. No amyloid was found in any organ.

Culture of the lung at autopsy yielded Staphylococcus aureus, coagulase-positive. No growth was obtained from the heart blood.

Final Anatomical Diagnosis: Multiple myeloma with involvement of bone marrow and spleen; toxic hepatitis caused by urethan; petechial hemorrhages in the gastric mucosa; toxic nephrosis probably caused by urethan; icterus; ascites (3600 cc.); bronchopneumonia (S. aureus); aspiration of gastric contents; pleural adhesions, fibrous left; appendectomy, postoperative, old.

COMMENT

This patient died in coma with rapidly increasing jaundice following 10½ months of treatment with urethan for multiple myeloma. At autopsy myeloma-cell infiltration was extensive in the bone marrow and slight in the spleen, with no other demonstrable visceral foci. There was no amyloidosis. The liver showed massive and diffuse acute centrilobular necrosis. The kidneys revealed diffuse tubular epithelial injury consisting of marked cytoplasmic dispersion, which appeared reversible. A search was made for the characteristics of myeloma nephrosis (dense casts in the distal convoluted tubules, tubular atrophy, and syncytitial-cell reaction to the casts), but none of these features was found. On the basis of the clinical and autopsy findings, the terminal illness is regarded as hepatic failure produced by urethan toxicity.

Toxic hepatitis induced by urethan has been described previously in five patients with multiple myeloma. These observations are supported by animal experiments in which extensive liver-cell degeneration was produced with this drug. Hepatic lesions in both patients and experimental animals resemble closely those encountered in our case. The mechanism by which urethan produces hepatic cell injury is not clear. From observations of lesions produced in experimental animals, it has been suggested that damage to the endothelium of the sinusoids and efferent veins initiates the hepatic lesion.[1] In our patient no evidence of primary endothelial injury was noted.

The presence of diffuse acute tubular epithelial damage in the kidneys of our patient is unusual, and it is unfortunate that no clinical laboratory studies are available to indicate the extent of the functional impairment produced by these changes, which morphologically appear reversible. The lesion differed from the alterations found in the kidney in association with multiple myeloma. There was no evidence of tubulorhexis or of cholemic nephrosis. The combination of hepatocellular and renal epithelial injury in this patient treated with urethan over a long period of time suggests that the renal tubular changes represent another effect of urethan toxicity.

SUMMARY

Massive centrilobular hepatic necrosis and diffuse toxic tubular damage were found at autopsy in a 39-year-old patient who died with hepatic failure. The patient had been treated for proved multiple myeloma for 10½ months with urethan in therapeutic doses. The hepatic and renal lesions are attributed to urethan.

REFERENCES

1. Doljanski, L., and Rosin, A.: Histology of the Rat's Liver in Urethane Poisoning, Am. J. Path. **20**:945, 1944.

2. Ohler, R.; Houghton, J. D., and Melaney, W. C.: Urethane Toxicity, New England J. Med. **243**:984, 1950.

3. Hazlett, B.; Taylor, H. E., and Whitelaw, D. M.: Fulminating Hepatic Necrosis in a Patient with Multiple Myeloma Treated with Urethane, Blood **10**:76, 1955.

4. Rundles, R. W.; Dillon, M. L., and Dillon, E. S.: Multiple Myeloma: Effect of Urethane Therapy, J. Clin. Invest. **29**:1243, 1950.

5. Meacham, G. C.; Tillotson, F. W., and Heinle, R. W.: Liver Damage After Prolonged Urethane Therapy, Am. J. Clin. Path. **22**:22, 1952.

6. Klima, R., and Wengraf, G.: Damage to the Central Nervous System by Urethan, Wien. med. Wchnschr. **99**:109, 1949.

7. Bell, E. T., and Kirschbaum, A.: Induction of Renal Glomerular Lesions by Urethane in Inbred Mice Susceptible to Spontaneous Glomerulonephritis, Proc. Soc. Exper. Biol. & Med. **64**:71, 1947.

News and Comment

ANNOUNCEMENTS

Graduate Fortnight.—The New York Academy of Medicine announces its 28th annual Graduate Fortnight, Oct. 10-21, 1955.

The program follows:

PROBLEMS OF AGING

6 Morning Panel Meetings—Afternoon Hospital Clinics—20 Evening Lectures
4 Evening Panel Meetings—Scientific Exhibit

EVENING LECTURES and PANEL MEETINGS at 8:30 P. M.

First Week

October

10 **OPENING ADDRESS**—Edward J. Donovan, *President, The New York Academy of Medicine*

WHAT IS AGING? *(Ludwig Kast Lecture)*
Albert Lansing, *Emory University School of Medicine, Atlanta*

PSYCHOLOGICAL ASPECTS OF AGING
Ross A. McFarland, *Harvard University*

EXPERIMENTAL PROLONGATION OF THE LIFE SPAN
Clive M. McCay, *Cornell University, Ithaca, N. Y.*

11 **ARTHRITIS IN THE ELDERLY PATIENT**
Joseph J. Bunim, *National Institute of Arthritis and Metabolic Diseases, Bethesda, Md.*

THE EFFECT OF AGING ON THE MYOCARDIUM
William Dock, *State University of New York College of Medicine at New York City, Brooklyn*

FLUID AND ELECTROLYTE PROBLEMS IN SURGERY OF THE AGED
Henry T. Randall, *Memorial Center for Cancer and Allied Diseases*

RELATION OF INCREASED LONGEVITY TO NEOPLASIA
C. P. Rhoads, *Memorial Center for Cancer and Allied Diseases*

12 **SOME PHYSIOLOGICAL ASPECTS OF AGING** *(Wesley M. Carpenter Lecture)*
N. W. Shock, *National Heart Institute, Bethesda, Md.*

NUTRITIONAL PROBLEMS OF ADVANCING AGE
Fredrick J. Stare, *Harvard University*

GASTROINTESTINAL HEMORRHAGE IN ELDERLY PATIENTS
Thomas P. Almy, *Cornell University Medical College*

13 **PANEL MEETING—CEREBROVASCULAR DISEASE WITH AGING**
Chairman: Irving S. Wright, *Cornell University Medical College*

14 **PANEL MEETING—PROBLEMS OF RETIREMENT**
Chairman: Howard Reid Craig, *Director, The New York Academy of Medicine*

Second Week

October

17 **THE NATURE OF THE RESPONSE TO STRESS WITH AGING**
(Harlow Brooks Lecture)
JAMES L. WHITTENBERGER, *Harvard University*

EVALUATION AND PREPARATION OF THE PATIENT WITH DEGENERATIVE CARDIOVASCULAR DISEASE FOR MAJOR SURGERY
JOHN S. LA DUE, *New York Hospital*

THE AGING LUNG
DICKINSON W. RICHARDS, *College of Physicians and Surgeons, Columbia University*

18 **MANAGEMENT OF INJURIES IN THE AGED**
ROBERT H. KENNEDY, *Beekman-Downtown Hospital, New York*

MANAGEMENT OF SURGICAL EMERGENCIES IN THE AGED
CONDICT W. CUTLER JR., *Goldwater Memorial Hospital, New York*

SURGERY OF CHRONIC DISEASES IN THE AGED
FRANK GLENN, *New York Hospital*

ANESTHESIA IN THE AGED
EMANUEL M. PAPPER, *Presbyterian Hospital*

19 **EMOTIONAL AND PSYCHIATRIC PROBLEMS OF AGING**
FRANCIS J. BRACELAND, *The Institute of Living, Hartford, Conn.*

NEUROSURGICAL TREATMENT OF PARKINSONISM
IRVING S. COOPER, *New York University–Bellevue Medical Center*

REHABILITATION IN THE AGED
HOWARD A. RUSK, *New York University–Bellevue Medical Center*

20 **PANEL MEETING—GONADAL FUNCTION AND INVOLUTION IN MAN—AND RELATED PRACTICAL MANAGEMENT**
Chairman: EARL T. ENGLE, *College of Physicians and Surgeons, Columbia University*

21 **PANEL MEETING—DISORDERS OF THE SPECIAL SENSE ORGANS ASSOCIATED WITH AGING: THEIR RECOGNITION AND TREATMENT**
Chairman: CHARLES F. WILKINSON JR., *New York University–Bellevue Medical Center*

MORNING PANEL MEETINGS—11:00 to 12:30

Monday, Oct. 10

AGING AND ATHEROSCLEROSIS .....*Chairman:* HENRY S. SIMMS

Wednesday, Oct. 12

EVERYDAY PROBLEMS IN THE CARE OF THE AGED
Chairman: FREDERIC D. ZEMAN

Friday, Oct. 14

MANAGEMENT OF CARDIOVASCULAR RENAL PROBLEMS IN THE AGED .....*Chairman:* HUGH LUCKEY

Monday, Oct. 17

MANAGEMENT OF PROSTATIC OBSTRUCTION
Chairman: ROBERT S. HOTCHKISS

Wednesday, Oct. 19

PUBLIC HEALTH ASPECTS OF AGING ..*Chairman:* W. G. SMILLIE

Friday, Oct. 21

PROBLEMS OF INFECTIOUS DISEASES AND THEIR THERAPY IN THE AGED .....*Chairman:* PERRIN H. LONG

All physicians as well as nonmedical but interested persons concerned with the problems of aging will be welcome as participants. All inquiries regarding fees and requests for registration should be addressed to Secretary, Graduate Fortnight, The New York Academy of Medicine, 2 East 103 St., New York 29.

Congress of Neurological Surgeons.—The Congress of Neurological Surgeons will hold its annual meeting at the Los Angeles Statler Hotel in Los Angeles, Oct. 27, 28, and 29, 1955. Information regarding details may be obtained from the secretary, Dr. Philip D. Gordy, 1007 Delaware Ave., Wilmington, Del.

Books

Emotional Problems and What You Can Do About Them. By William B. Terhune, M.D. Price, $3.00. Pp. 190. William Morrow & Co., Inc., 425 Fourth Ave., New York 16, 1955.

This book is essentially a primer directed to the lay public. It is divided into two major parts, the first dealing with the fundamentals of personal mental hygiene and the second with techniques for meeting specific psychologic emergencies. The author points out many of the signposts of emotional instability and attempts to elaborate constructive criteria related to preventive psychologic measures. The book stresses the negation of detrimental attitudes and places strong emphasis on a positive approach to life situations.

It appears that the only preventive value in the book is the help it may give to people to suspect some emotional difficulty in their present lives. The reviewer fails to see how physicians, clergymen, social workers, or the lay public can derive anything constructive from this book, because of its superficial, yet dogmatic, approach to emotional problems. It seems that the author is feebly attempting to structure a series of commandments that all persons are to follow strictly if they are to achieve emotional maturity. This is not only poor psychologic thinking but also an improper application of sound psychologic principles.

Viral and Rickettsial Diseases of the Skin, Eye and Mucous Membranes of Man. By Harvey Blank, M.D., and Geoffrey Rake, M.D. Price, $8.50. Pp. 285, with 62 illustrations. Little, Brown & Company, 34 Beacon St., Boston 6, 1955.

The writers in their preface state the reason for this book: "It has seemed to the present authors that these diseases and disease manifestations form a logical field of interest which could be well covered in monographic form, and the present volume is the result." The authors, experts in the field, have done an excellent job; the monograph is well written, well and profusely illustrated, and finely printed on good paper. The discussions are up to date, and there are excellent bibliographies. It is of interest that chicken pox and zoster are taken up together, although the elaborate chapter on herpes simplex is separate. Measles, German measles, roseola, infectious mononucleosis, dengue, fourth disease, and fifth disease are thrown into one chapter. The book is highly satisfying.

Die Tuberkulose in der ärztlichen Praxis. By Dr. Med. A. Wernli-Haessig. Price, $5.55. Pp. 154, with 52 illustrations and 7 tables. S. Karger, Holbeinstrasse 22, Basel, Switzerland; 215 Fourth Ave., New York 3, 1954.

This book presents eleven papers given at the fifth postgraduate course of the Zurich Kantonal League Against Tuberculosis, in March, 1954.

It is available in the United States through Albert J. Phiebig, P. O. Box 352, White Plains, N. Y.

After an introduction by Wernli-Haessig, the papers deal with superinfection, treatment of the tubercular patient at home, epidemiology, methods of examination, and advancement in the pathological anatomy of tuberculosis of the lungs.

The second half contains new methods of findings, staining, and culturing the tubercle bacillus and discussion of its development of resistance against drugs. This is followed by articles about the tuberculosis problem in patients over 50 years of age, the present state of BCG vaccination, limitations of chemotherapy, indications for the surgical treatment of cavities, and, finally, selected chapters of the history of tuberculosis.

The section about chemotherapy is particularly interesting. It describes in detail the "Schaukel therapy" which means the administration of 300 mg. of isoniazid (INH) daily in combination with streptomycin, 1 gm. every third day, and 10 to 12 gm. of *p*-aminosalicylic acid on two out of three days. The author believes that this scheme offers the best way to avoid the development of resistance of the tubercle bacillus.

Year Book of Medicine (1954-1955 Year Book Series). Edited by P. B. Beeson, M.D.; C. Muschenheim, M.D.; W. B. Castle, M.D.; T. R. Harrison, M.D.; F. J. Ingelfinger, M.D., and P. K. Bondy, M.D. Price, $6.00. Pp. 711, with 115 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1955.

The number of medical communications and the number of journals in which they appear increases year by year. No one person or small group of persons could possibly read this voluminous literature and condense it for digestion by the average medical practitioner. Many compendia and abstract services are available which attempt to help the conscientious physician in this dilemma—none being entirely satisfactory. The Year Books probably solve the difficulty better than any of the others.

In the latest "Year Book of Medicine" a group of carefully chosen editors makes a good selection from the periodical medical literature of 1953 and first part of 1954. It is unlikely that any important development in a subject of major importance is neglected. The papers reported are well condensed but, for the most part, not diluted. Comments by the editors are pertinent and helpful. For the internist trying to keep up with new developments of the past few years perusal of the Year Book in its entirety will make an adequate supplement to the current reading of the two or three periodicals with which he attempts to keep up fairly complete and current contact.

Year Book of Drug Therapy (1954-1955 Year Book Series). Edited by Harry Beckman, M.D. Price, $6.00. Pp. 592, with 74 illustrations. Year Book Publishers, Inc., 200 E. Illinois St., Chicago 11, 1955.

Internists who find the "Year Book of Medicine" a useful library addition will be equally rewarded by reading the 1954-1955 "Year Book of Drug Therapy." The selection of the year's outstanding contributions in this important field by a single person is a tremendous task. We are greatly indebted to Dr. Beckman for his careful summaries and the editorial comments which, because of his well-known background in pharmacology, he is able to make with authority and fairness.

As one compares this latest compendium with those of the two or three years immediately preceding it he is struck by the decrease in contributions on corticotropin (ACTH) and cortisone and the increase in reports of the deleterious effects of antibiotics—especially the sensitivity reactions to penicillin and the serious effects of dislocations of bacterial flora from antibiotic therapy, such as those due to ascendency of resistant staphylococci and Candida albicans.

There are numerous articles on the pros and cons of relatively new drugs such as 6-mercaptopurine in leukemia, erythromycin and carbomycin, N-allylnormorphine, chlorpromazine, new anticoagulants, new antihypertensive drugs, and phenylbutazone. Fortunately many accounts of serious reactions to the latter drug are included and emphasized. For a survey of recent developments in drug therapy most internists will find this volume invaluable.

Diagnostic Laboratory Hematology. By George E. Cartwright, M.D. Price, $3.00. Pp. 102, with 6 illustrations. Grune & Stratton, Inc., 381 Fourth Ave., New York 16, 1954.

Dr. Cartwright has presented in compact form a manual for the guidance of house officers and practitioners in the laboratory diagnosis of hematologic disorders. He has chosen one method for each examination, using the criteria of "simplicity, accuracy, reliability, time of performance, cost, and availability of equipment." Not only are adequate instructions provided for each determination, but comments on sources of error, interpretation, and indications for further procedures are also included.

It is surprising, however, that the author has entirely omitted ABO and Rh typing, the Coombs test, and the heterophile agglutination yet included other, less frequently indicated procedures. Despite his excellent coverage of tests for urine and stool pigments related to hemoglobin, he has not included the van den Bergh test.

The user of this manual should find it a valuable, convenient, and time-saving source of information. Some of the procedures presented are not usually thought of as "commonly used" in everyday practice, but perhaps this book will encourage physicians to avail themselves of more of the hematologic diagnostic procedures than are commonly used at present, since most of those included can be performed with the usual equipment of a small laboratory.

The Ciba Collection of Medical Illustrations: Volume 2. Reproductive System. By Frank H. Netter, M.D. Price, not given. Pp. 286, with 223 illustrations. Ciba Pharmaceutical Products, Inc., 510 Morris Ave., Summit, N. J., 1954.

Ciba Pharmaceutical Products, Inc., has done a real service to medicine in publishing this atlas on the reproductive system. It is a most complete survey of the anatomy and pathology of the male and the female reproductive system, of pregnancy, of the mammary gland, and, finally, of intersexuality.

The book is listed as having 223 plates. Almost none consist of a single drawing. Most have three to five drawings to the plate. All are in color and are magnificent. Frank H. Netter is a physician as well as an artist. His drawings are simple and clear but at the same time not too diagrammatic.

The drawings of microscopic preparations of various types of testicular failure are particularly beautiful and at first seem superior to those made from tumors of the female genital tract. In all probability this difference is due to the better quality of the preparations from the testes. Most of these were probably made for research purposes, while the latter were routine preparations.

Numerous consultants, including S. A. Vest, J. A. Gaines, Isadore Rubin, Somers Sturgis, and Nick Assoli, prepared various sections of the text and helped checking in the accuracy of the drawings.

The reviewer thinks this atlas should be highly recommended and believes it would be of interest and of value to the readers of the ARCHIVES.

Medical Treatment of Mental Disease. By D. J. McCarthy, M.D., and K. M. Corrin, M.D. Price, not given. Pp. 653, with 30 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Montreal, 1955.

There are certain aspects of this very long treatise which will meet with general approval. It is one, however, which will satisfy neither the psychiatrically oriented internist nor the psychiatrist who is at the same time a good doctor. In the corpus of the book there is a remarkable failure to separate demonstrated fact from belief. This is particularly true where many pharmacologic agents, analeptics, vitamins, and so forth are recommended wholeheartedly for the treatment of various conditions. Evidence of any controlled study to illuminate this therapeutic jungle land is lacking. There is great need for a book to clarify the frequently beclouded central terrain which exists between psychiatry and general medicine. This book, keeping close to the orthodox views of the past, fails to satisfy the need.

Regional Enteritis: Diagnostic and Therapeutic Considerations. By Frederick F. Boyce, M.D. Price, not given. Pp. 84, with 9 illustrations. J. B. Lippincott Company, 227-231 S. 6th St., Philadelphia 5; Aldine House, 10-13 Bedford St., London, W.C. 2; 2083 Guy St., Boston 6, 1955.

This little booklet presents an unbiased review of some of the literature related to the etiology, pathology, diagnosis, and therapeutic considerations of regional enteritis.

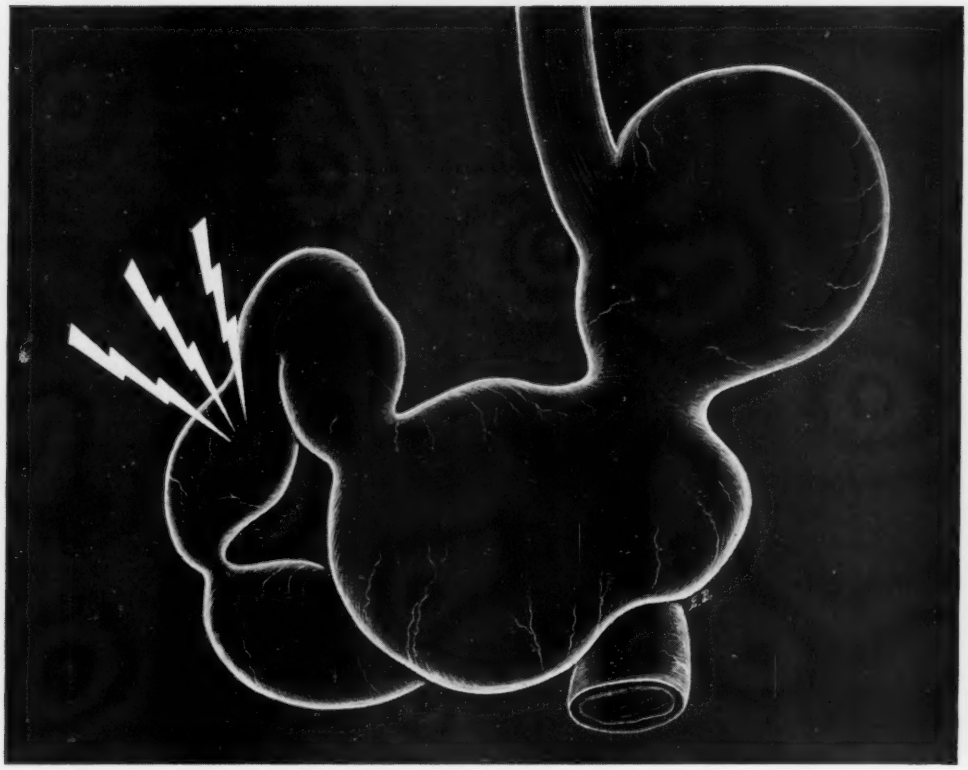
Although it contains no original contributions, it should prove of value to those who wish a quick, concise summary of the disease. It is well outlined and organized. The chapter on the disease in children is especially good.

The Kidney: A Ciba Foundation General Symposium. Edited by A. A. G. Lewis, M.D., and G. E. W. Wolstenholme. Price, not given. Pp. 352, with 125 illustrations. J. & A. Churchill, Ltd., 104 Gloucester Place, Portman Sq., London W. 1, 1954.

This volume records the proceedings of an international symposium on the Kidney held in London in 1953, including outstanding investigators from this country and western Europe. The formal presentations covered a wide range of subjects, for example, aspiration biopsy of the kidney, the renal lesions related to amino-aciduria, the mechanism of osmotic work of the tubules, biochemical aspects of tubular transport, factors in renal glycosuria, renal regulation of acid-base balance and potassium excretion, postoperative retention of water and sodium, calcium and phosphorus excretion, and renal factors in the control of volume of body fluid.

At the end of each chapter is a general informal discussion, in which many interesting questions are raised and differences in point of view expressed. While much of the material in this volume has been published previously in the scientific literature, this symposium summarizes clearly the major current lines of thought and evidence in the field of renal physiology, and their applications to human disease. It is, therefore, a valuable contribution and will provide stimulation to inquiring minds.

PRO-BANTHINE FOR ANTICHOLINERGIC ACTION



Abnormal Motility as the Cause of Ulcer Pain

Until recently the general opinion was held that ulcer pain was primarily caused by the presence of hydrochloric acid on the surface of the ulcer.

Present investigations[1,2] on the relationship of acidity and muscular activity to ulcer pain have led to the following concept of its etiologic factor:

"... abnormal motility[2] is the fundamental mechanism through which ulcer pain is produced. For the production and perception of ulcer pain there must be, one, a stimulus, HCl or others less well understood; two, an intact motor nerve supply to the stomach and duodenum; three, altered gastro-duodenal motility; and four, an intact sensory pathway to the cerebral cortex."

Pro-Banthine® has been demonstrated consistently to reduce hypermotility of the stomach and intestinal tract and in most instances also to reduce gastric acidity. Dramatic remissions[1] in peptic ulcer have followed Pro-Banthine therapy. These remissions (or possible cures) were established not only on the basis of the disappearance of pain and increased subjective well-being but also on roentgenologic evidence.

Pro-Banthine Bromide (Beta-diisopropylaminoethyl xanthene-9-carboxylate methobromide, brand of propantheline bromide) has other fields of usefulness, particularly in those in which vagotonia or parasympathotonia is present. These conditions include hypermotility of the large and small bowel, certain forms of pylorospasm, pancreatitis and ureteral and bladder spasm.

1. Schwartz, I. R.; Lehman, E.; Ostrove, R., and Seibel, J. M.: A Clinical Evaluation of a New Anticholinergic Drug, Pro-Banthine, Gastroenterology *25*:416 (Nov.) 1953.

2. Ruffin, J. M.; Baylin, G. J.; Legerton, C. W., Jr., and Texter, E. C., Jr.: Mechanism of Pain in Peptic Ulcer, Gastroenterology *23*:252 (Feb.) 1953.

SEARLE

A NEW SERIES IN

SEX EDUCATION

Titles in the new series

- PARENTS' PRIVILEGE
  for parents of young children of pre-school and early school age
- A STORY ABOUT YOU
  for children in grades 4, 5, and 6
- FINDING YOURSELF
  for boys and girls of approximately junior high school age
- LEARNING ABOUT LOVE
  for young people of both sexes (about 16 to 20 years of age)
- FACTS AREN'T ENOUGH
  for adults who have any responsibility for children or youth that may create a need for an understanding of sex education

PRICES

Note: Discounts apply to quantities of any single title, or to quantities of sets.

Quantity	Discount	Price
1	—	$ .50
10	10%	4.50
25	30%	8.75
50	40%	15.00
100	50%	25.00
1000	60%	200.00

Set of 5 titles, $2.25.

Distributed by

AMA SERVICES
Box No. 8610A
Chicago 77, Ill.

ORDER BLANK

Enclosed is $_____(no stamps) for the following pamphlet(s):

Title	Quantity
1. PARENTS' PRIVILEGE	
2. A STORY ABOUT YOU	
3. FINDING YOURSELF	
4. LEARNING ABOUT LOVE	
5. FACTS AREN'T ENOUGH	
Complete set of five	

Please send pamphlet(s) to:
(Please Print)

Name_____

Street_____

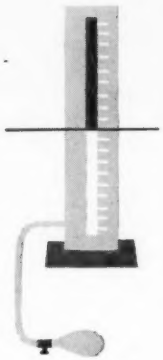
City_____

Zone_____ State_____

IM 8-55

from a new study:

'Dexedrine' "does not bring about a significant or sustained rise in blood pressure when the dose is kept within the normal clinical range (5 to 20 mg. daily)."[1]



no significant rise in blood pressure

Dr. Roberts administered 'Dexedrine' to 76 patients suffering from hypertension complicated by obesity or depression. Frequent blood pressure readings were taken. At the end of a 2-year study, she concluded:

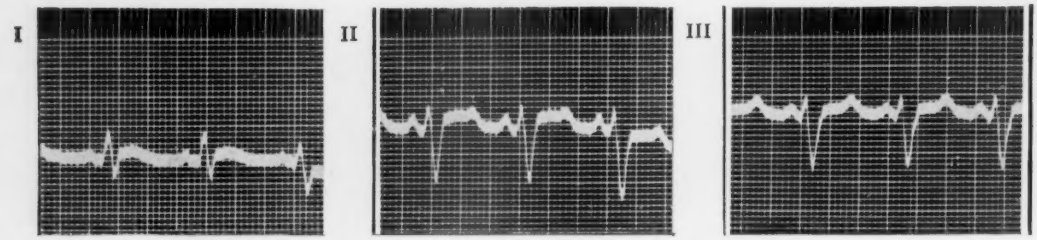
'Dexedrine' . . . "is not contraindicated in patients suffering from benign hypertension."

Dexedrine* Sulfate
(dextro-amphetamine sulfate, S.K.F.)

Tablets • Elixir
Spansule† capsules

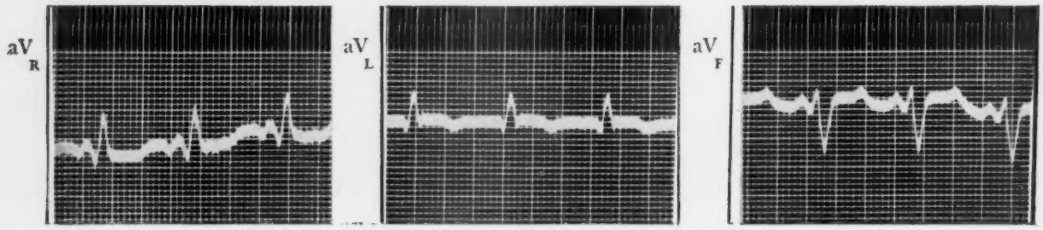
Smith, Kline & French
Laboratories, Philadelphia

1. Roberts, E.: Am. Pract. & Dig. Treat. 5:606.
* T.M. Reg. U.S. Pat. Off.
† T.M. Reg. U.S. Pat. Off. for S.K.F.'s brand of sustained release capsules.
Patent Applied For



REDUCE MORTALITY

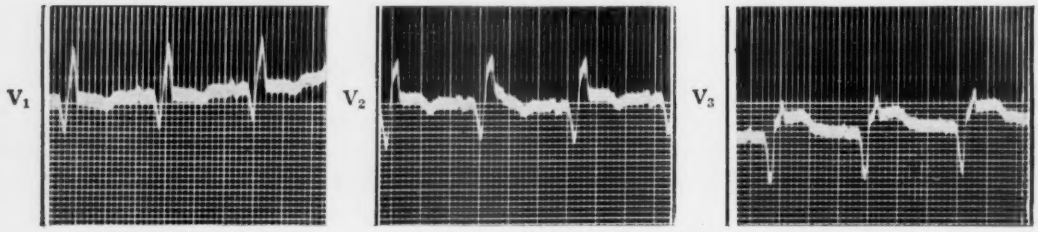
in Myocardial Infarction with *Severe Shock*



by the early use of

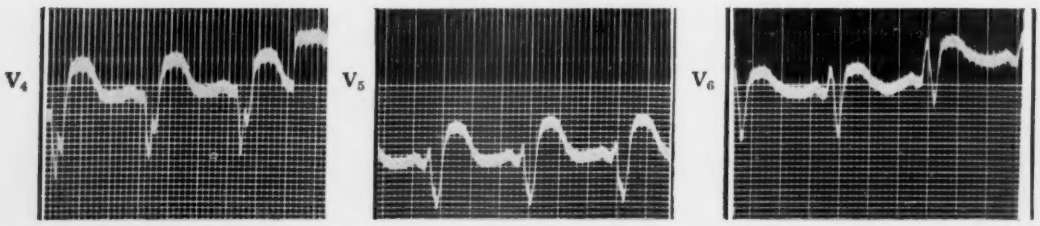
LEVOPHED®

the most powerful pressor antidote for shock



Levophed bitartrate 0.2% solution in ampuls of 4 cc., boxes of 10, to be administered in 1000 cc. of 5% dextrose solution in distilled water or 5% dextrose in saline solution.

Winthrop-Stearns INC.
NEW YORK 18, N. Y. WINDSOR, ONT.

Write for detailed literature.

Levophed, trademark reg. U. S. Pat. Off., brand of levarterenol